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**SCREENING FOR CARDIOVASCULAR RISK FACTORS IN MIDDLE-AGED MEN:
THE LONG-TERM EFFECT OF LIFESTYLE COUNSELLING**

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ACADEMIC DISSERTATION

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Reijo Siren

LIST OF ABBREVIATIONS

AHA	The American Heart Association
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CT	Computed tomography
CVD	Cardiovascular disease
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
ECG	Electrocardiography
ESC	The European Society of Cardiology
FINDRISC	Finnish Diabetes Risk Score
hs-CRP	High-sensitivity C-reactive protein
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment for insulin resistance
IDF	The International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
LDL-C	Low-density lipoprotein cholesterol
LTPA	Leisure-time physical activity
MetS	Metabolic syndrome
MHO	Metabolically healthy obese
MHOW	Metabolically healthy overweight
MR	Magnetic resonance
NPV	Negative predictive value
OR	Odds ratio
PA	Physical activity
PPV	Positive predictive value
PUFA	Polyunsaturated fatty acid
ROC	Receiver operating characteristics
RR	Relative risk
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
SFA	Saturated fatty acid

TC	Total cholesterol
TG	Triglycerides
T2D	Type 2 diabetes
VAT	Visceral adipose tissue
WC	Waist circumference

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, designated in the text by Roman numerals. In addition, previously unpublished data are presented.

- I. Siren R, Eriksson JG, Vanhanen H. Waist circumference a good indicator of future risk for type 2 diabetes and cardiovascular disease. *BMC Public Health* 2012 Aug 9;12:631-2458-12-631.
- II. Granér M, Siren R, Nyman K, Lundbom J, Hakkarainen A, Pentikainen MO, Lauerma K, Lundblom N, Adiels M, Nieminen MS, Taskinen MR. Cardiac steatosis associates with visceral obesity in nondiabetic obese men. *J Clin Endocrinol Metab* 2013 Mar;98(3):1189–1197.
- III. Siren R, Eriksson JG, Peltonen M, Vanhanen H. Impact of health counselling on cardiovascular disease risk in middle-aged men: influence of socioeconomic status. *PLoS One* 2014 Feb 14;9(2):e88959.
- IV. Siren R, Eriksson JG, Vanhanen H. Observed changes in cardiovascular risk factors among high-risk middle-aged men who received lifestyle counselling: a 5-year follow-up. *Scand J Prim Health Care* 2016 Dec;34(4):336–342.

1 ABSTRACT

Mortality from coronary heart disease (CHD) among the working-age population has declined by 70% during the past 50 years in Finland. Factors contributing to this development include both advances in health policy and the improvement of medical care. Despite this favourable trend, cardiovascular disease (CVD), especially ischaemic heart disease, is still the leading cause of death among the working-age male population in Finland. One of the substantial risk factors for CVD and type 2 diabetes is obesity, predominantly abdominal – that is the accumulation of fat in the visceral adipose tissue. When the subcutaneous adipose tissue's ability to store fat is exceeded, the excess fat accumulates in the visceral adipose tissue and ectopic depositions in organs, such as skeletal muscles, liver, pancreas, and heart. This aberrant fat accumulation strongly correlates with an adverse cardiometabolic profile.

We studied the association between visceral adiposity and cardiac steatosis in 70 non-diabetic obese middle-aged men. The amount of visceral adipose tissue, abdominal subcutaneous tissue and epicardial and pericardial fat depositions was measured by magnetic resonance imaging. Cardiac steatosis correlated with the amount of abdominal subcutaneous fat tissue and visceral adiposity; the correlation was stronger with visceral adiposity. Furthermore, of all the cardiometabolic risk factors measured, WC correlated strongest with visceral adiposity as well as epicardial and pericardial fat.

WC is an indirect measure, but it is considered to be a reliable measure of visceral adiposity. Thus, it can serve as a tentative means when assessing the risk for CVD and type 2 diabetes. To study the predictive value of WC to assess the risk for CVD and type 2 diabetes in middle-aged men, we used data from 200 men from a community-based screening programme in the city of Helsinki. Our results show that a cut-off point for a WC of ≥ 94 cm identifies those with increased risk for CVD and/or type 2 diabetes with a sensitivity of 84.4% and specificity of 78.2%.

Yearly, from 2006 onwards, all men aged 40 living in Helsinki have been invited to a CVD risk evaluation and health counselling visit at their local healthcare centre. Men who were found to be at high risk received lifestyle counselling aiming at risk reduction. We conducted two prospective follow-up studies among the men who were at high risk in the year 2006 screening. In the first study, our aim was to

determine whether the impact of lifestyle counselling on health behaviour and total CVD risk during the two years of follow-up depended on educational attainment. In 2008, a total of 430 initially high-risk men were identified and invited to a follow-up visit; 200 participated. Subjects were categorised into three groups according to their educational attainment: low (≤ 9 years), middle (10 to 12 years) and high (≥ 13 years). We observed a positive trend in lifestyles in all three groups. In the low educational attainment group, the change in lifestyle did not lead to a significant reduction in the overall risk for CVD, whereas the risk reduction was statistically significant in the two higher educational attainment groups during follow-up.

In our second prospective study, we aimed to determine whether the continuation of risk communication would lead to and sustain lifestyle changes and maintain the possibly achieved lower CVD risk during the five-year follow-up. In 2011, a total of 389 initially high-risk men were identified and invited to a follow-up visit; of these, 159 participated. We observed that the participants' self-reported lifestyles improved regardless of the continuation of risk communication, while the overall risk for CVD improved only among those who were continuing risk communication during the five-year follow-up.

If lifestyle behaviour has not been optimal during early adulthood, a person may have been exposed to one or more CVD risk factors before reaching middle age. Often, an easily recognisable indication of such exposure is abdominal obesity. In everyday practice in primary healthcare, abdominal obesity and a low level of education should trigger a comprehensive risk evaluation and, when appropriate, an offer of health counselling. Achieving sustainable lifestyle changes and risk reduction requires ongoing risk communication between parties.

2 TIIVISTELMÄ

Työikäisen väestön sepelvaltimotautikuolleisuus on 50 viime vuoden aikana vähentynyt Suomessa 70%. Myönteiseen kehitykseen on vaikuttanut tietoinen pyrkimys tupakoinnin vähentämiseen sekä elintapojen kautta väestön kolesterolipitoisuuksien pienentämiseen ja verenpainetasojen madaltamiseen. Nämä muutokset selittävät yli puolet kuolleisuuden vähentymisestä, hoitojen tehostuminen sekä kehitys loput. Huolimatta myönteisestä kehityksestä sydän- ja verisuonitaudit ovat edelleen yleisin työikäisten miesten kuolinsyy Suomessa.

Yksi merkittävä sydän- ja verisuonisairauksille ja tyypin 2 diabetekselle altistava riskitekijä on lihavuus, erityisesti vyötärölihavuus, joka heijastaa ylimääräisen rasvan kertymistä vatsaonteloon. Kun ihonalaisen rasvakudoksen kyky varastoida rasvaa ylittyy, vatsaonteloon kertyvän rasvan lisäksi rasvaa varastoituu luustolihaksiin, maksaan, haimaan ja sydämeen. Tämä ei-toivottu sisäelimiin kertyvä rasva korreloi vahvasti haitallisen metabolisen riskiprofiilin kanssa.

Selvitimme tutkimuksessamme diabetesta sairastamattomien lihaviiden miesten sydämen rasvoittumisen ja vatsaonteloon kertyneen rasvan määrän suhdetta sydän- ja verisuonitautiriskitekijöihin

Rasvan määrä vatsaontelossa, vatsan alueen ihonalaisessa kudoksessa ja sydämessä mitattiin magneettikuvauksella. Sydämen rasvoittuminen korreloi sekä vatsan alueen ihonalaisen rasvakudoksen että vatsaonteloon kertyneen rasvan määrään, voimakkaammin jälkimmäiseen. Kaikista mitatuista metabolisista riskitekijöistä vyötärön ympärysmitta korreloi voimakkaimmin vatsaontelon sisäisen rasvan määrään ja sydämen rasvoittumiseen.

Vyötärön ympärysmitta on epäsuora, mutta luotettavaksi osoitettu vatsaonteloon kertyneen rasvan mittari. Sitä voidaan käyttää alustavana keinona arvioitaessa riskiä sairastua sydän- ja verisuonitauteihin sekä tyypin 2 diabetekseen.

Toisessa tutkimuksessamme selvitimme vyötärön ympärysmittan kykyä löytää valikoimattomasta keski-ikäisten miesten joukosta miehet, joiden riski sairastua sydän- ja verisuonitauteihin sekä tyypin 2 diabetekseen oli suurentunut. Aineistomme koostui kahdestasadasta keski-ikäisestä helsinkiläismiehestä, jotka olivat osallistuneet Helsingin kaupungin terveyskeskuksen järjestämään riskiseulontaan. Tulokset osoittivat, että vyötärön ympärysmittan raja-arvo ≥ 94 cm

erottaa osallistujien joukosta ne, joiden riski sairastua sydän- ja verisuonitauteihin tai tyyppin 2 diabetekseen on riskiprofiilin perusteella lisääntynyt. Kyseistä raja-arvoa käyttämällä menetelmän herkkyys oli 84,4% ja tarkkuus 78,2%.

Vuodesta 2006 alkaen on vuosittain kutsuttu kaikki Helsingissä asuvat kyseisenä kalenterivuonna 40 vuotta täyttävät miehet sydän- ja verisuonitautiriskien arviointiin ja terveysneuvontaan paikalliseen terveyskeskukseen. Miehillä, joiden riskin todetaan suurentuneen, annetaan elintapaneuvontaa, jonka tavoitteena on riskin pienentäminen. Toteutimme kaksi seurantatutkimusta miehillä, joilla vuoden 2006 seulonnassa todettiin lisääntynyt sydän- ja verisuonitautien riski. Ensimmäisen tutkimuksen tavoitteena oli selvittää elintapaneuvonnan vaikutusta sydän- ja verisuonitautien kokonaisriskiin kahden vuoden seurannassa niin, että osallistujien koulutustaso otettiin huomioon. Vuonna 2008 miehistä, joiden riski oli todettu suureksi, tavoitettiin 430. Heidät kutsuttiin seurantakäynnille, ja 200 noudatti kutsua. Osallistujista muodostettiin koulutustason mukaan kolme ryhmää. Elintavat muuttuivat suotuisammiksi kaikissa kolmessa ryhmässä. Alimman koulutustason ryhmässä elintapojen muutokset seuranta-aikana eivät kuitenkaan johtaneet merkitsevään sydän- ja verisuonitautien kokonaisriskin pienenemiseen toisin kuin kahdessa korkeamman koulutustason ryhmässä.

Toisessa seurantatutkimuksessa selvitimme viiden vuoden seuranta-aikana omaehtoisesti toistettujen riskinarviointitapaamisten vaikutusta pienemmän riskin saavuttamiseen ja ylläpitoon. Vuonna 2011 miehistä, joiden riski oli seulonnassa alun perin todettu suureksi, tavoitettiin 389. Heidät kutsuttiin seurantakäynnille, ja kutsua noudatti 159 miestä. Tulokset osoittivat, että elintavat olivat muuttuneet suotuisaan suuntaa riippumatta siitä, oliko riskejä arvioitu uudelleen seuranta-aikana. Muutos oli tilastollisesti merkitsevä. Kuitenkin vain seuranta-aikana uudelleen riskinarvioinnissa käyneiden sydän- ja verisuonitautiriski pieneni.

Altistuminen epäedullisten elintapojen vaikutuksille alkaa jo lapsuudessa ja jatkuu aikuisikään, jolloin viimeistään todetaan muutokset myös biologisissa riskitekijöissä. Usein ensimmäinen ulkoinen merkki altistumisesta voi olla keskivartalolihavuus. Päivittäisessä vastaanottotyössä olisi tärkeää käynnistää laajempi sydän- ja verisuonisairauksien riskikartoitus kaikille keskivartalolihaville sekä sosioekonomiselta asemaltaan heikommille. Samalla olisi tärkeää tukea riskienhallintaakin. Saavutettujen elintapamuutosten ja pienemmän riskin ylläpitäminen edellyttää palveluiden tuottajien ja käyttäjien yhteydenpidon jatkuvuutta.

3 INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. Almost one-third (31%) of all deaths among men younger than 65 in Europe were caused by CVD according to WHO's Mortality Database update in February 2014 ⁽¹⁾. The Global Burden of Disease Study 2010 identified the top-eight risk factors contributing to the Global Burden of Disease. In Europe, these are, in descending order: tobacco smoking, high blood pressure (BP), high body mass index (BMI), alcohol use, physical inactivity, high fasting plasma glucose, a diet low in fruit and high total cholesterol ⁽²⁾. The European Guidelines on CVD prevention in clinical practice contain the same behavioural risk factors ⁽³⁾. The four main behavioural risk factors for CVD identified by the World Health Organization (WHO) are tobacco smoking, an unhealthy diet, physical inactivity and the harmful use of alcohol ⁽⁴⁾. A healthy lifestyle adopted in early adulthood and sustained throughout life protects individuals from CVD ⁽⁵⁾. However, lifestyle changes in middle age still have the potential to reduce the risk of CVD. In a cohort study of adults aged 45 to 64 who engaged in a healthy lifestyle (i.e. diet high in fruits and vegetables, regular exercise, BMI 18.5–29.9 kg/m² and not smoking) CVD events and mortality were reduced significantly in the four-year follow-up compared to people with less healthy lifestyles ⁽⁶⁾. In the U.S. Health Professionals Follow-up Study, men who adopted at least two new healthy lifestyle factors during the follow-up significantly decreased their relative risk of coronary heart disease (CHD) compared with men who did not change their unhealthy lifestyle ⁽⁷⁾. The preventive potential of modifiable behavioural risk factors in the middle-aged and older population is considerable. The cross-sectional population-based survey of adults aged 40 to 79 shows that only 16% of the study's population was free from behavioural risk factors (i.e. daily smoking, physical inactivity, low fruit intake, high alcohol consumption and obesity), while 45% had at least two of these behavioural risk factors ⁽⁸⁾.

Primary healthcare has a significant role in supporting population strategies to reduce the risk for CVD by promoting a healthy lifestyle in the general public. As primary healthcare provides most public health services, it can identify those who are at high risk and implement preventive measures. There are clinical guidelines to facilitate the assessment and management of CVD risk in primary healthcare. According to these guidelines, expert organisations recommend beginning

systematic total CVD risk assessments in men at age 40 and in women at age 50^(3,9). However, it has been shown that there are shortcomings in the implementation of guidelines in general practice. In the primary prevention of a high-risk asymptomatic population, risk factors remain uncontrolled for a large proportion⁽¹⁰⁾, and healthier lifestyle promotions have not progressed properly. Consequently, risk factor targets were poorly achieved^(11,12). Although the majority of physicians support the use of guidelines, only half apply them in their everyday practice⁽¹³⁾.

Accordingly, the objective of this thesis is to evaluate whether the screening of CVD risk factors among men age 40 combined with lifestyle counselling for those at high risk is beneficial from a long-term risk management perspective.

4 REVIEW OF THE LITERATURE

‘The scale and pattern of disease reflect the way that people live and their social, economic, and environmental circumstances, and all of these can change quickly’. On page 35 of *The Strategy of Preventive Medicine* by Geoffrey Rose (1992).

4.1 Cardiovascular disease

Cardiovascular disease (CVD) is defined as a group of disorders of the heart and blood vessels, including CHD, cerebrovascular disease, elevated BP, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure.

CVD causes more deaths globally than any other non-communicable disease group. CHD and stroke are the major components of CVD. The World Health Organization (WHO) has estimated that the total number of deaths from CVD was 17.7 million in 2015 globally. These include CHD being responsible for 7.4 million deaths and stroke being responsible for 6.7 million deaths ⁽⁴⁾. The corresponding figures for Europe were 4 million in total, 1.8 million from CHD and 1 million from stroke, respectively ⁽¹⁴⁾. There are striking differences in age-adjusted CVD mortality rates between European countries; the highest mortality rates are seen in Eastern Europe. They are almost tenfold higher than the lowest rate in Western Europe ⁽¹⁴⁾. In Finland, age-standardised CHD mortality has decreased continuously over the past 40 years, a trend that continued in 2015. During the same time period, the median age of people who died of CHD increased from 65 years to 79 years among men and from 73 years to 87 years among women. In 1971, nearly four out of ten of those who died of CHD were of working age, while in 2015, the corresponding figure was one out of ten ⁽¹⁵⁾.

4.2 Historical perspectives on preventive cardiology

The epidemiological approach to CVD can be considered to have begun in the 1940s. Among the first studies was a prospective study of professional men in Minnesota. The 15-year follow-up indicated an association between CHD mortality and total cholesterol ⁽¹⁶⁾. This research was followed by the Seven Countries Study,

another prospective study, in which the 25-year follow-up results confirmed the association between total cholesterol and CHD ⁽¹⁷⁾. The results also showed a positive association between BP and CHD ⁽¹⁸⁾. The results from the U.S. Railroad cohort of the Seven Countries Study during a 40-year period demonstrated significant associations between CVD and smoking, systolic blood pressure (SBP) and serum cholesterol ⁽¹⁹⁾. Importantly, the Seven Countries Study revealed this relationship was not dependent on culture. Simultaneously, the Framingham Heart Study (FHS) provided further evidence on the importance of BP, cholesterol and cigarette smoking in the development of CHD ^(20,21,22). The Whitehall study ⁽²³⁾ increased the general knowledge of CVD risk factors, myocardial ischaemia and CHD death. Based on the observation that the number of risk factors and their simultaneous occurrence is directly related to the incidence of CHD, the investigators of the FHS were the first to introduce the concept of a global risk assessment for CHD ^(24,25). There are several other important epidemiological studies that have been conducted over the past 70 years that have contributed to establishing the practices of preventive cardiology based on risk factors and risk assessment. The largest of these studies was The Monica Project ⁽²⁶⁾, the publications of which expose the trends of CHD risk factors in various populations and the contributions of these trends to event rates and CHD mortality. The Interheart study ⁽²⁷⁾, conducted globally, showed that the same large pattern of risk factors was consistently associated with myocardial infarction worldwide in all ethnic groups and in both sexes.

4.3 Risk factors for CVD

There is a broad consensus concerning the major risk factors for CVD. Risk factors are classified as modifiable and non-modifiable. Non-modifiable risk factors include sex, age, race and family history of CVD. Major modifiable risk factors include physical inactivity, tobacco exposure, unhealthy diet, obesity and harmful use of alcohol, high BP, dyslipidaemia and type 2 diabetes ⁽²⁸⁾. Besides modifiable risk factors, other risk factors include low socioeconomic status, psychosocial stress, depression and anxiety.

4.4 Behavioural risk factors

During recent decades, evidence from epidemiological research has shown the importance of lifestyle factors concerning the development of diseases. Regarding CVD, the main contributing behaviours are harmful use of alcohol, tobacco smoking, unhealthy diet and physical inactivity.

4.4.1 Diet

A diet rich in saturated fat, trans-fats and salt, and low in fruits, vegetables and fish is linked to increased cardiovascular risk ⁽²⁹⁾. The Seven Countries Study was the first large cohort study that investigated the association between diet and CVD. Food consumption patterns varied highly between the study populations in the 1960s ⁽³⁰⁾. Twenty-five years of follow-up showed the diversity of dietary patterns had markedly different consequences respecting CHD mortality. A diet low in animal and dairy products and rich in plant food seemed to be protective against CHD on the population level ⁽³¹⁾. A dietary pattern characteristic of Greece and other parts of the Mediterranean region was called the *Mediterranean diet* ⁽³¹⁾. The Mediterranean diet is characterised by the high intake of plant food and olive oil; moderate intake of fish and poultry; low intake of dairy products, red meats, processed meats and sweets; and wine consumed in moderation with meals ⁽³²⁾. In prospective population-based research with a median follow-up of 44 months, higher degree adherence to a Mediterranean diet was associated with significantly lower total mortality, mortality from CHD and mortality from cancer, hazard ratios being 0.75 (95% CI 0.64–0.87), 0.67 (95% CI 0.47–0.94) and 0.76 (95% CI 0.59–0.98), respectively ⁽³³⁾. A meta-analysis of 34 prospective cohort studies including over 4 million people demonstrated that a two-point increase in the adherence to the Mediterranean diet resulted in an 8% reduction in overall mortality, a 10% reduction in mortality and incidence of CVD, a 6% reduction in mortality and incidence of cancer and a 13% reduction in neurodegenerative disease ⁽³⁴⁾. In work based on the Epic–Norfolk prospective cohort, a higher adherence to the Mediterranean-style diet turned out to be effective in reducing CVD incidence and mortality, even beyond the Mediterranean region ⁽³⁵⁾. In a randomised secondary prevention trial (Lyon Diet Heart Study), the Mediterranean diet (enriched with alpha-linolenic acid) proved to be more effective than the usually recommended post-infarct diet to prevent recurrent cardiac events. During a mean follow-up of 27

months after a first myocardial infarction, the risk ratio for the composite outcomes including cardiac death and non-fatal myocardial infarction was 0.27 (95% CI 0.12–0.59), indicating a 73% risk reduction in the intervention group compared to the control group ⁽³⁶⁾. After a mean follow-up of 46 months, authors confirmed that the protective effect of the Mediterranean diet was maintained as a risk ratio, for the composite outcome was 0.28 (95% CI 0.15–0.53) ⁽³⁷⁾. In a primary prevention study (Predimed study), subjects with high cardiovascular risk but no CVD at enrolment were randomly assigned to one of three groups: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts and a control diet (participants in control group was advised to reduce dietary fat) ⁽³⁸⁾. After a median follow-up of 4.8 years, the findings indicated that the Mediterranean diet supplemented with extra-virgin olive oil or mixed nuts reduced the incidence of major cardiovascular events (myocardial infarction, stroke or death from cardiovascular causes) by 30% compared to the control diet.

There is an ongoing large, randomised CVD primary prevention trial (Predimed-Plus) that is focusing on multiple lifestyle factors: the Mediterranean diet, physical activity and weight control ⁽³⁹⁾. The study's investigators have reported the effectiveness of an intensive lifestyle intervention on weight-loss and cardiovascular risk factors in 626 overweight/obese adults with metabolic syndrome aged 55–75 years ($n = 626$). The lifestyle intervention is based upon an energy-restricted Mediterranean diet, physical activity promotion and behavioural support. The intervention group includes 327 participants, with 299 in the control group, respectively. At the 12 months' follow-up, the average weight loss in the intervention group was 3.2 kg, and in the control group, 0.7 kg. A weight loss $\geq 5\%$ was achieved by 33.7% of the participants in the intervention group and by 11.9% in the control group. The improvement of cardiovascular risk factors was greater in the intervention group compared to the control group ⁽⁴⁰⁾.

4.4.2 Physical activity

Epidemiological studies have shown that physical inactivity is an independent risk factor for both CVD and all-cause mortality ^(41,42,43). The main types of physical activities that have been focused upon in studies regarding this topic are work-related, commuting and leisure-time physical activities (LTPA). Morris and colleagues researched bus drivers in the 1950s ⁽⁴⁴⁾, and Paffenbarger and colleagues investigated dockworkers in the 1970s ⁽⁴⁵⁾, all demonstrating that physical activity

at work has a protective effect against CHD mortality. Supporting findings were obtained in several other studies examining the relationship of CHD to physical activity, whether work or leisure. Such studies were summarised in a review article published in 1987 ⁽⁴⁶⁾, and in a meta-analysis published in 1990 ⁽⁴⁷⁾. Both of these reports conclude that the literature at that time revealed consistent evidence of an inverse association between physical activity and the incidence of CHD. Accumulated evidence led the American Heart Association in 1992 to identify physical inactivity as a risk factor for CVD ⁽⁴⁸⁾. In 1996, the U.S. Surgeon General highlighted the health benefits of moderate daily physical activity for both sexes and all ages ⁽⁴⁹⁾. In 2008, the U.S. Department of Health and Human Services (HHS) released their Physical Activity Guidelines for Americans ⁽⁵⁰⁾. In 2010, the WHO followed this publication with their Global Recommendations on Physical Activity on Health' ⁽⁵¹⁾. Both organisations recommend a minimum of 150 minutes a week of moderate-intensity physical activity or 75 minutes a week of aerobic vigorous-intensity physical activity. Even greater health benefits can be achieved by increasing the amount of weekly physical activity. The recommendation has since been widely adopted in national recommendations around the world. In 'European Guidelines on CVD Prevention in Clinical Practice', the recommendations for physical activity are consistent with the abovementioned bodies ⁽³⁾. A meta-analysis published in 2011 reported that subjects who maintained the level of 150 minutes per week of moderate-intensity LTPA have a relative risk for CHD of 0.86 (95% CI 0.77–0.96) compared to sedentary subjects. Of those who maintained a level of 300 minutes per week of moderate-intensity LTPA, the corresponding relative risk was 0.80 (95% CI 0.74–0.88 ⁽⁵²⁾. The HHS released their second edition of Physical Activity Guidelines for Americans in 2018. The recommendation for weekly moderate and vigorous intensity of physical activity remained unchanged. Furthermore, the recommendation highlights additional health benefits from muscle-strengthening activities at least two times a week. Unlike the previous recommendation, any duration of episodes can be included in the accumulated total volume of physical activity ⁽⁵³⁾.

4.4.3 Smoking

Over 7 million people die each year because of smoking. Direct smoking causes more than 6 million of these deaths, and about 890,000 deaths are caused by the exposure to second-hand smoke among non-smokers ⁽⁵⁴⁾. Smoking prevalence varies considerably from one country to another. In Europe, within the population

aged 15 years and over, the lowest prevalence of daily smokers was reported in Sweden at 11.9%, while the highest prevalence of daily smokers was reported in Greece and Turkey at 27.3% in 2014 ⁽⁵⁵⁾. In Finland, the prevalence of daily smoking among men and women in the age group of 20 to 64 years was 15% and 13%, respectively, in 2018, and the trend is declining ⁽⁵⁶⁾.

Even in the 1930s, the hazardous effect of tobacco smoking on life expectancy was demonstrated by Raymond Pearl ⁽⁵⁷⁾. A prospective study of British male doctors showed that excess deaths attributable to cigarette smoking were mainly caused by ischaemic heart disease, lung cancer, chronic obstructive lung disease and atherosclerotic vascular disease ⁽⁵⁸⁾. Results of 50 years of follow-up of the same cohort revealed that smokers lived on average about 10 years less than non-smokers. However, smoking cessation at ages 60, 50, 40 or 30 extends life expectancy by about three, six, nine and 10 years, respectively ⁽⁵⁹⁾.

In 2000, in the industrialised world, the leading cause of deaths attributable to smoking was CVD (0.75 million male deaths and 0.27 million female deaths), accounting for 42.1% of all smoking-attributable deaths ⁽⁶⁰⁾. Besides active cigarette smoking, exposure to environmental tobacco smoke and the use of snuff increased the risk for CVD. A meta-analysis of 19 epidemiological studies demonstrated that people who have never smoked had 30% greater risk for ischaemic heart disease (IHD) at age 65 if they have lived with a smoker. For those smoking 20 cigarettes a day, the corresponding risk was 78% ⁽⁶¹⁾. The relative risk for heart disease of those who have never smoked due to exposure to environmental tobacco smoke at work was assessed in a meta-analysis of eight prospective studies ⁽⁶²⁾. According to the results, the exposure to environmental tobacco smoke in the workplace increased the risk for IHD by 21% compared to those who have never smoked without workplace exposure. In an analysis with a follow-up of 12 years, the relative risk of death from CVD was 1.4 among snuff users, 1.8 among moderate smokers and 1.9 among heavy smokers, respectively, compared to non-smokers ⁽⁶³⁾. The habitual use of e-cigarettes has two consequences associated with increased CVD risk: a sympathetic dominance in cardiac autonomic balance and increased oxidative stress ^(64,65).

4.4.4 Alcohol

Morbidity as well as individual and societal suffering are well-known consequences of abundant alcohol use. According to a WHO report, over 3 million

deaths can be attributed to the excessive use of alcohol, representing 5.3% of all deaths in 2016 globally. Alcohol-attributable deaths are more marked in relatively young age groups; in the age group 20–39, such deaths represent 13.5% of total deaths ⁽⁶⁶⁾. In Finland, alcohol-related diseases and accidental alcohol poisoning caused 13.7% of all deaths in the working-age population in 2015 ⁽⁶⁷⁾. Though deaths from alcohol-related causes have decreased from 2008 onwards, the number of deaths from alcohol-related causes was still greater in 2015 than from any neoplasm or IHD ⁽⁶⁶⁾. Observational studies have shown a dose-dependent relationship between alcohol consumption and cardiovascular mortality, giving the dependency graph a J-shaped curve. Compared to abstinence or heavy drinking, the protective effect concerning CVDs and mortality is achieved with moderate alcohol consumption. In a cohort study of more than 67,000 men and women, 15 years of follow-up showed that men with an alcohol intake of 15–20 g/day had a hazard ratio of 0.75 for cardiovascular deaths and women with an alcohol intake of 10–15 g/day had a hazard ratio of 0.69 for cardiovascular deaths compared to abstainers. Alcohol intake lower or higher than those indicated had higher hazard ratios for cardiovascular deaths ⁽⁶⁸⁾. A meta-analysis of a total of 116,702 subjects depicted no threshold between alcohol consumption and the risk for 14 diseases (neoplasm and non-neoplasm diseases). A dose-dependent J-shaped relationship was discovered only for CHD with a minimum relative risk of 0.80 when alcohol consumption was 20 g/day ⁽⁶⁹⁾. An even greater risk reduction has been found in some studies. According to a case-control study, the risk for the first non-fatal myocardial infarction was lowest when alcohol intake was 5 to 9.9 g/day, with the odds ratio being 0.44, compared with lifelong abstainers ⁽⁷⁰⁾.

The causality between the moderate use of alcohol and lower risk for CVD is explained by an ethanol-induced increase in insulin sensitivity ⁽⁷¹⁾, increase in high-density cholesterol ^(72,73) and positive changes in haemostatic factors ⁽⁷²⁾. However, the cardio-protective effect is rapidly lost through negative metabolic consequences when the amount of alcohol used increases ⁽⁷⁴⁾. Because it is not predictable for whom drinking will become problematic, the beginning of alcohol consumption should not be recommended to anyone in a preventive sense ^(75,76). Until problem drinkers can be identified and the balance of beneficial and harmful effects can be considered, physicians should apply more innocuous interventions to prevent CHD ^(77,78). Furthermore, the results of recent studies challenge the health benefits of the moderate alcohol consumption advanced by previous work. Based on the results of a 31-year follow-up, Martin-Diener et al. ⁽⁷⁹⁾ introduced a chart for the survival

probability over the next 10 years of subjects aged 65 and 75 years depending on four behavioural risk factors: smoking, fruit intake, leisure-time physical activity and alcohol consumption. The chart illustrates that moderate alcohol consumption did not improve survival probabilities for any behavioural risk factor combination compared to abstainers. The high use of alcohol was associated with a lower 10-year survival probability compared with abstainers and moderate drinkers. A Mendelian randomisation meta-analysis of 56 epidemiological studies including 260,000 individuals calls into question the beneficial effect of light-to-moderate alcohol consumption, suggesting that reductions of alcohol consumption at all levels may be beneficial for cardiovascular health ⁽⁸⁰⁾.

4.5 Metabolic risk factors

The main metabolic risk factors contributing to CVD include BP, elevated cholesterol, diabetes and obesity. Each alone at non-optimal levels increases the CVD risk; the effect is additive, as these factors form a cluster.

4.5.1 Blood pressure

High BP is a major risk factor for CHD ⁽⁸¹⁾. In 2015, globally, 4.9 million (54.5%) of all CHD deaths and 90.1 million (55.1%) of all disability-adjusted life years (DALYs) were attributable to an SBP ≥ 110 –115 mmHg. With an SBP ≥ 140 mmHg, the corresponding numbers were 3.6 million (40.1%) for CHD deaths and 61.7 million (37.6%) for DALYs, respectively ⁽⁸²⁾.

A study with a median follow-up of 5.2 years in a cohort of 1.25 million people indicated that the lowest risk for CVD was among those with an SBP between 90 and 114 mmHg and DBP between 60 and 74 mmHg. In addition, those with a BP $\geq 140/90$ mmHg and those receiving BP-lowering medication had a lifetime risk of CVD at 30 years of 63.3% compared with a lifetime risk of 46.1% among those with a normal BP. Furthermore, among those with a normal BP, CVD was diagnosed five years later ⁽⁸³⁾.

The overall burden of hypertension is declining. Worldwide data showed that, in the adult population, 26.6% of men and 26.1% of women had hypertension in 2000 ⁽⁸⁴⁾, while the corresponding figures were 24.1% in men and 20.1% in women in

2015, respectively. In Finland, in a random population-based sample, 40.7% of men and 22.4% of women had hypertension in 2012 ⁽⁸⁵⁾. It is recognised that the risk of BP-related CVD increases well below the traditional threshold (140/90 mm Hg) for drug treatment.

At the population level, the optimal prevention of BP-related CVD is achieved through lifestyle changes. A meta-analysis of prospective cohort studies, with a median follow-up of 9.5 years and including more than 136,000 persons initially free from hypertension, demonstrates that high and moderate levels of leisure-time PA were associated with a decreased risk of hypertension. Those with high levels of PA had a 19% reduction in the risk of hypertension, and those with a moderate level of PA had a 11% reduction in the risk of hypertension compared to those with low levels of PA ⁽⁸⁶⁾. A meta-analysis of 54 randomised controlled trials suggests that aerobic exercise was associated with a significant reduction in mean systolic and diastolic BP. The BP reduction was statistically significant in both hypertensive and normotensive participants ⁽⁸⁷⁾. Typically, a single dietary factor has only a modest effect on BP. However, the combined effect of multiple dietary factors can be substantial. The most effective diet for controlling BP is the DASH diet, a diet rich in fruits, vegetables and low-fat dairy products with a reduced content of saturated and total fat. In a study comparing the effect of a typical American diet (control), a diet rich in fruit and vegetables and the DASH diet on BP, the DASH diet reduced SBP by 5.5 mmHg and DBP by 3.0 mmHg compared to a control diet. The corresponding reduction with the diet rich in fruit and vegetables was 2.8 mmHg in SBP and 1.1 mmHg in DBP, respectively ⁽⁸⁸⁾. Another study compared the effect of a typical American diet (control) with the DASH diet, both diets combined with three levels of sodium intake: high = 3.3 g/day, intermediate = 2.5 g/day and low = 1.5 g/day. The reduction of salt consumption had a markedly greater effect on BP in the control diet than in the DASH diet. Differences in SBP between diets were statistically significant in all sodium categories, but in DBP, a statistical significance was not achieved in the low sodium category. The maximum difference of -8.9 mmHg in SBP was seen between diets in comparing the control diet with the high sodium category to the DASH diet with the low sodium category corresponding figure in DBP was -4.5 mmHg. The variations in BP between groups or between dietary sodium categories are shown in Figure 1 ⁽⁸⁹⁾.

In Finland, the intake of sodium among men aged 25–64 years was 3.5 g/day and among women 2.6 g/day in 2012. National recommendations are ≤ 2.8 g/day and ≤ 2.4 g/day, respectively ⁽⁹⁰⁾.

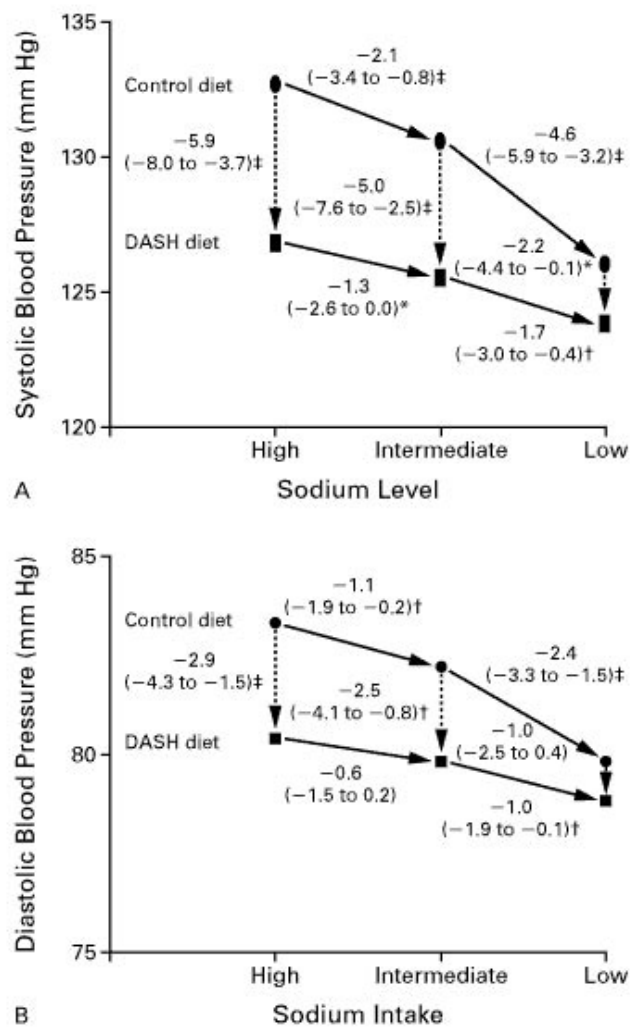


Figure 1. The effect of systolic blood pressure (Panel A) and diastolic blood pressure (Panel B) of reduced sodium intake and the DASH diet (Reproduced with permission from reference ⁽⁸⁹⁾. Copyright Massachusetts Medical Society). Asterisks (P<0.05), daggers (P<0.01) and double daggers (P<0.001) indicate significant distinctions in BP between groups or between dietary sodium categories.

4.5.2 Overweight and obesity

BMI is a commonly used measure to indicate an association between weight and the risk of diseases. BMI is a person's weight in kilograms divided by the square of height in metres (kg/m^2). A Belgian scientist, Adolphe Quételet, initially proposed BMI in the middle of the 1800s, and it was initially called the *Quetelet index*.

Table 1. Adult BMI categories according to the WHO ⁽⁹¹⁾

Underweight	BMI < 18.5 kg/m^2
Normal weight	BMI 18.5 kg/m^2 to 24.9 kg/m^2
Overweight	BMI 25.0 kg/m^2 to 29.9 kg/m^2
Obesity class I	BMI 30.0 kg/m^2 to 34.9 kg/m^2
Obesity class II	BMI 35.0 kg/m^2 to 39.9 kg/m^2
Obesity class III	BMI \geq 40 kg/m^2

In 2015, globally, a total of 107.7 million (5%) children and 603.7 million (12%) adults were obese. Among adults, a BMI of 25 kg/m^2 or more contributed to 4 million deaths, representing (7.1%) of all deaths globally. Of all deaths associated with a BMI of above 25 kg/m^2 , CVD was the leading cause of death. Moreover, 23.9% of all deaths among overweight persons and 41% of all deaths among obese persons were due to CVD ⁽⁹²⁾. Likewise, the prevalence of obesity is rising in Europe and has tripled since the 1980s ⁽⁹³⁾.

In 2012, in a population survey of 8,600 Finns aged 25 to 74 years, the prevalence of normal weight in men was 29.9%, overweight 49.1% and obesity 23.4%. In women, the figures for normal weight were 36.8%, 38.6%, and 23.8%, respectively ⁽⁹⁴⁾.

Data from a meta-analysis of 239 prospective studies, including over 10 million participants from Asia, Australia, New Zealand, Europe and North America, showed that all-cause mortality was lowest at a BMI between 20 kg/m^2 and 25 kg/m^2 . All-cause mortality increased significantly below that range and throughout

all ranges of both overweight and obesity. Another analysis excluded the first five years of follow-up and was restricted to those who never smoked without pre-existing chronic disease, counting almost 4 million participants having BMIs above 25 kg/m². In this work, all-cause mortality and mortality involving CHD, stroke, respiratory disease and cancer increased progressively with increasing BMI ⁽⁹⁵⁾. Contrary to the study above, findings from a review of 97 studies with 2.9 million participants suggested that, in relation to normal weight, obesity class 1 with a BMI of 30 kg/m² to 34.9 kg/m² was not associated with excess all-cause mortality. Overweight with a BMI of 25 kg/m² to 29.9 kg/m² was associated with lower all-cause mortality ⁽⁹⁶⁾. Notably, this study drew criticism for methodological biases like reverse causation and confounding by smoking ^(97,98).

Increasing body weight is related to known CVD risk factors including hypertension, dyslipidaemia and insulin resistance.

A study of 243,798 subjects (57% men) with a mean follow-up of 14.1 years indicated that the prevalence of hypertension, diabetes and hypercholesterolaemia raised with increasing BMI. Among overweight and obese individuals without risk factors, the risk for CVD mortality was not significantly higher compared with normal-weight individuals without risk factors. The association of overweight with hypercholesterolaemia increased the risk for the CVD mortality hazard ratio (HR) by 1.45 (95% CI 1.13 to 1.86) in men. A similar increase in the risk was not observed in women. A greater increase in the risk of CVD death was seen when overweight was associated with hypertension – that is HR 2.05 (1.71 to 2.46) in men and 2.15 (1.48 to 3.11) in women. The risk of CVD deaths increased considerably in overweight subjects with both hypertension and hypercholesterolaemia or both hypertension and diabetes, with an HR: 2.65 (95% CI 2.20 to 3.19) and 3.01 (95% CI 2.29 to 3.95) in men, as well as 2.57 (95% CI 1.80 to 3.68) and 4.50 (95% CI 2.67 to 7.58) in women, respectively. A more significant increase in risk was observed in men, but not in women, when overweight was associated with all three risk factors: hypertension, diabetes and hypercholesterolaemia, with an HR: 3.67 (95% CI 2.78 to 4.85) in men, as well as 2.87 (95% CI 1.60 to 5.13) in women, respectively ⁽⁹⁹⁾.

Individuals differ in their metabolic responses to adiposity. Those with a diagnosis of overweight and obesity, based on BMI, but who lack most of the metabolic abnormalities have been called *metabolically healthy overweight* (MHOW) or *metabolically healthy obese* (MHO).

In a study of 22,203 men and women (45.2% men) with an average follow-up of seven years, 24% of the participants were defined as obese. Among them, 22% were categorised as MHO. Subjects were defined as metabolically healthy if they had a maximum of one metabolic abnormality: WC > 102 cm in men and > 88 cm in women; clinical BP > 130/85 mmHg, hypertension diagnosis, or use of antihypertensive medication; HDL cholesterol (< 1.03 mmol/l in men and < 1.30 mmol/l in women); physician-diagnosed diabetes; or low-grade inflammation (CRP \geq 3 mg/l). MHO was not associated with an increased risk of CVD compared with the metabolically healthy non-obese; the hazard ratio (HR) was 1.26 (95% CI 0.74 to 2.13). Both non-obese and obese participants with at least two metabolic abnormalities were at an increased risk: HR 1.59 (95% CI 1.30 to 1.94) and 1.64 (95% CI 1.17 to 2.30), respectively ⁽¹⁰⁰⁾.

Data from a meta-analysis of 14 studies with a total of 299,059 participants showed that MHOW and MHO individuals were at an increased risk of CVD events with a relative risk (RR) of 1.26 (95% CI 1.10 to 1.45) and 1.56 (95% CI 1.40 to 1.92), respectively, compared with healthy normal-weight participants. Correspondingly, there was an increased risk of CVD mortality with an RR of 1.30 (95% CI 1.07 to 1.58) in MHOW and 1.37 (95% CI 1.03 to 1.82) in MHO. The subgroup of MHOW participants with a follow-up < 15 years was not at an increased risk for CVD, with an RR of 1.05 (95% CI 0.94 to 1.18), whereas the subgroup with a follow-up > 15 years showed increased risk with an RR of 1.47 (95% CI 1.37 to 1.58). The MHO participants were at an increased risk of CVD in both subgroups (follow-up < 15 years and > 15 years), with an RR of 1.40 (95% CI 1.20 to 1.62) and 2 (95% CI 1.79 to 2.24), respectively ⁽¹⁰¹⁾.

A longitudinal study with a median follow-up of 30 years indicated that, regardless of BMI categories (normal weight, overweight and obese), subjects with MetS had a higher risk of both total and cardiovascular deaths as well as a greater risk for major CVD events than subjects without MetS in the same BMI category. In addition, those in the categories of overweight and obesity without MetS had a higher risk for major cardiovascular events and total deaths, compared to normal-weight men without metabolic derangements. The event rate was highest in obese subjects with MetS, HR for total deaths, cardiovascular deaths and major CVD events: 2.43 (95% CI 1.81–3.27), 3.20 (95% CI 2.12–4.82) and 2.55 (95% CI 1.82–3.58), respectively ⁽¹⁰²⁾.

Although BMI provides a practical measure of obesity, it is not as good as waist circumference (WC) to assess metabolically active intra-abdominal fat. WC is easy to measure in a clinical setting, and it is strongly correlated to abdominal fat mass, subcutaneous fat and intra-abdominal fat, as measured by computed tomography (CT) ⁽¹⁰³⁾.

In a study of 1,106 participants with a mean follow-up of 6.1 years, CT determined the adipose tissue volume of the participants. The results showed that an additional 500 cm³ increase in fat volume was associated with an incident hypertension, the odds ratio (OR): 1.21 for subcutaneous adipose tissue (SAT); OR: 1.30 for visceral adipose tissue (VAT), hypercholesterolaemia OR:1.10 for SAT; OR: 1.37 for VAT, hypertriglyceridemia OR:1.15 for SAT; OR: 1.56 for VAT, and metabolic syndrome OR:1.43 for SAT; OR:1.82 for VAT, respectively ⁽¹⁰⁴⁾.

BMI and WC complement each other in the assessment of adiposity-associated cardiometabolic risk. Results from the large international cross-sectional study IDEA show that, in all BMI categories (normal weight, overweight and obese), a 1-SD increase in WC was associated with a significantly higher risk of CVD and type 2 diabetes. Among those men with a normal weight, the CVD risk increased by 10%, among the overweight by 19% and among the obese by 23%, among the women the CVD risk increased by 15%, 12%, and 24%, respectively. Among those men with a normal weight, the risk of type 2 diabetes increased by 27%, among the overweight by 23% and among the obese by 34%, among the women the risk of type 2 diabetes increased by 43%, 32% and 43%, respectively ⁽¹⁰⁵⁾.

Data from the Health Professionals Follow-Up Study of 27,270 men demonstrates the combined effect of overall and abdominal obesity on the risk of type 2 diabetes. By taking as a reference group those with a BMI < 25 kg/m² and WC < 90 cm at baseline, in each BMI category (<25 kg/m², 25 kg/m² to 29 kg/m² and ≥30 kg/m²), an increased WC (<90 cm, 90 cm to 99 cm and ≥100 cm) predicted a greater risk of type 2 diabetes during the 13-year follow-up ⁽¹⁰⁶⁾.

4.5.3 Dyslipidaemia

Dyslipidaemia is defined as elevations of fasting total cholesterol (TC) concentration which may or may not be associated with elevated triglyceride (TG) concentration. As lipids are not water soluble, they are transported in plasma in

particles known as *lipoproteins* ⁽¹⁰⁷⁾ of which the two most relevant for everyday practice are low-density lipoprotein (LDL) and high-density lipoprotein (HDL).

Dyslipidaemia can occur due to hereditary factors, but more commonly, it is an acquired condition. Dietary fatty acids and cholesterol affect serum TC and LDL-cholesterol as follows: saturated fatty acids and cholesterol increase, polyunsaturated fatty acids decrease, and monounsaturated fatty acids have no independent effect on serum total cholesterol. The changes in LDL-cholesterol were parallel to those in serum total cholesterol, but changes in HDL-cholesterol remained uncertain ⁽¹⁰⁸⁾.

Elevated levels of blood lipids are well-documented risk factors for CVD. Findings from a 10-year follow-up study of middle-aged participants free from CHD at baseline showed that fasting LDL-C, HDL-C and TG are independent predictors of CHD. A 1-SD (1.05 mmol/l) increase of TC was associated with a 34% and 32% higher risk of CHD in men and in women, respectively. Correspondingly, a 1-SD (1mmol/l) increase of LDL-C was associated with a 42% and a 37% higher risk of CHD in men and women, respectively ⁽¹⁰⁹⁾.

A study including 5,794 subjects (53.5% women) with an average follow-up of 15 years showed that the RR of CHD with LDL-cholesterol levels between 130 mg/ml and 159 mg/ml (3.36 mmol/l to 4.11mmol/l) was 1.50 (95% CI 1.05 to 2.15) and with LDL-cholesterol levels \geq 160 mg/ml (4.13 mmol/l) RR was 2.04 (95% CI 1.44 to 2.90), respectively, compared to an LDL level < 130 mg/ml (3.36 mmol/l). Non-HDL-cholesterol (total cholesterol minus HDL-cholesterol) showed an even stronger association with the incidence of CHD than LDL-cholesterol ⁽¹¹⁰⁾.

Combined low HDL-cholesterol and high triglyceride levels are also associated with an elevated risk for CHD and stroke. A prospective study of 3,216 participants without CVD at baseline (40% men, 41% with diabetes) with a median follow-up time of 17.7 years showed that participants with combined high TG and low HDL-cholesterol levels had a 32% and a 46% greater hazard for CHD and for ischaemic stroke, respectively, than participants with normal TG and HDL-cholesterol levels. When the hazard ratio was assessed among those without diabetes, combined high TG and low HDL-cholesterol was not associated with a greater hazard for CHD or ischaemic stroke than combined normal TG and normal HDL-cholesterol. However, among the diabetics, combined high TG and low HDL-cholesterol was associated with a 54% and a 113% greater hazard for CHD and ischaemic stroke, respectively, compared to combined normal TG and HDL-cholesterol ⁽¹¹¹⁾.

A meta-analysis of 61 prospective observational studies with almost 900,000 participants with a mean follow-up of 13 years showed that a 1 mmol/l lower total cholesterol was associated with a 56%, 34% and 17% lower ischaemic heart disease (IHD) mortality in both sexes at ages 40–49, 50–69 and 70–89 years, respectively. HDL-cholesterol-related variables indicated that a 0.33 mmol/l higher HDL-cholesterol, a 1 mmol/l lower non-HDL-cholesterol and a 1.33 mmol/l lower total cholesterol/HDL-cholesterol were associated with a reduction in IHD mortality by one-third ⁽¹¹²⁾.

The effect of increased polyunsaturated fatty acid (PUFA) intake as a replacement for saturated fatty acid (SFA) on CHD endpoints was analysed using the pooled results of eight randomised controlled trials, including a total of 13,614 participants (21.2% with established CHD) with a median follow-up time of 4.25 years. In the intervention groups, the average PUFA consumption was 14.9% of total energy intake; in the control groups, average PUFA consumption was 5% of total energy intake. The results showed that, compared to the control group, the mean decrease in total cholesterol levels in the intervention group was 0.76 mmol/l, corresponding to a risk reduction of 24% for a 1 mmol/l reduction in TC. The overall CHD risk reduction was 19%, corresponding to a 10% less CHD risk for each 5% energy increment from PUFA. In four studies lasting less than 4.25 years and another four studies of at least 4.25 years, the pooled CHD risk reduction was 9% and 27%, respectively. In four studies evaluating primary prevention populations and another four studies evaluating secondary prevention populations, the pooled CHD risk reduction was 24% and 16%, respectively ⁽¹¹³⁾.

In a study of randomly assigned 174,149 participants (27% women) statin therapy reduced major vascular events by 24% per each 1 mmol/l reduction in LDL-cholesterol. The reduction was significant in both women and men. In a subgroup with no known history of vascular disease, the reduction was 25% and among those with a history of vascular disease 21%, respectively. Overall vascular mortality was reduced by 12% and deaths from unknown cause by 13% per each 1mmol/l LDL-cholesterol reduction. Deaths from non-vascular causes were reduced by 4% ⁽¹¹⁴⁾.

4.5.4 Impaired glucose homeostasis

Glucose homeostasis is the balance between insulin and glucagon secretion to maintain blood glucose. The consequences of balance disturbance are impaired fasting glucose, impaired glucose tolerance and type 2 diabetes.

It is estimated that, in 2015, among the global adult population aged 20–79 years, the number of people with diabetes was 415 million, a figure projected to rise to 642 million by 2040 ⁽¹¹⁵⁾. In 2016, there were about 300,000 people with type 2 diabetes in Finland and an additional estimated 150,000 undiagnosed cases ⁽¹¹⁶⁾.

Diabetes is associated with an increased risk of CHD. Analyses of data from prospective cohort studies with a duration of follow-up from four to 36 years revealed that people with diabetes had a rate of fatal CHD events of 5.4% and those without diabetes of 1.6%, respectively. Rates vary between sexes. The fatal event rate in women (with and without diabetes) was 7.7% and 1.2%, respectively. The corresponding event rates in men were 4.5% and 2.0%; see Figure 2.

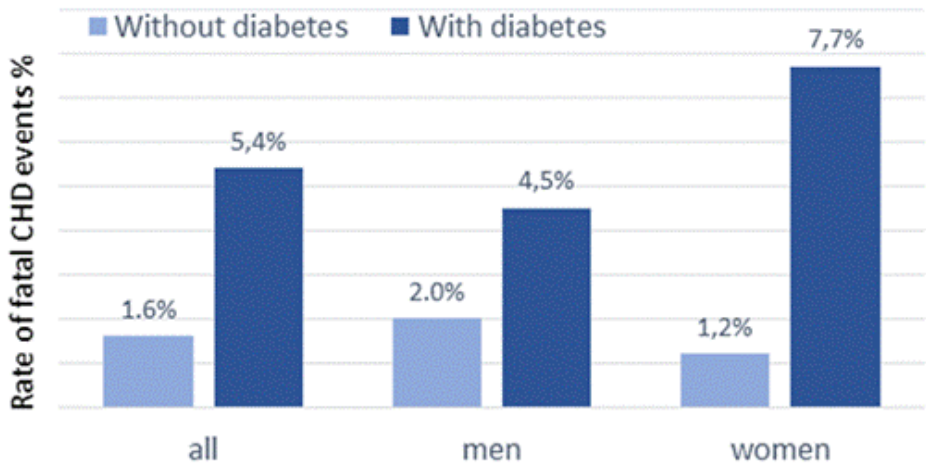


Figure 2. Difference in type 2 diabetes and fatal coronary heart disease events between men and women

Regarding RR, in women, the risk for a fatal CHD event was 3.5 (95% CI 2.70 to 4.53), and among men, 2.06 (95% CI 1.81 to 2.34) ⁽¹¹⁷⁾. A similar trend was reported in a study using data from the Emerging Risk Factors Collaboration databank. Analyses included data from people with and without diabetes. By comparing people with diabetes to people without diabetes, the hazard ratios for CHD were 1.89 (95% CI 1.73 to 2.06) in men and 2.59 (95% CI 2.29 to 2.93) in women, respectively. The corresponding hazard ratios for ischaemic stroke were

2.16 (95% CI 1.84 to 2.52) in men and 2.83 (95% CI 2.35 to 3.40) in women, respectively ⁽¹¹⁸⁾.

During a seven-year follow-up, there were no significant distinctions in the hazard ratios for fatal CHD between diabetic subjects without prior myocardial infarction and non-diabetic subjects with prior myocardial infarction. The hazard ratio was 1.2 (95% CI 0.6 to 2.4) when adjusted for age, sex, total cholesterol, hypertension and smoking. The result suggests an equal risk of myocardial infarction in the two groups ¹¹⁹. Like the previous work, a Danish register-based study demonstrated that diabetic individuals have a cardiovascular risk comparable to non-diabetics with prior myocardial infarction ¹²⁰.

There is also evidence of an association between pre-diabetes and an increased risk for CVD. Based on the results of a systematic review that included 175,152 people, the authors suggest that IFG and IGT are linked with a modest increase in the risk for CVD ⁽¹²¹⁾. Meta-analyses of 20 studies with a mean follow-up of 12.4 years including 95,783 non-diabetic people indicated that fasting and postprandial hyperglycaemia are associated with CVD. A fasting plasma glucose level of 6.1 mmol/l, the threshold value for IFG and a 2-h glucose level of 7.8 mmol/l, the threshold value for IGT were associated with a 30% and 58% increase in risk for a cardiovascular event, respectively, compared to a fasting glucose level of 4.2 mmol/l ⁽¹²²⁾.

The results of a study comparing intensive lifestyle intervention and lifestyle advice only among persons with IGT disclose that, although the intensive lifestyle intervention reduced the incidence of type 2 diabetes, it did not lessen cardiovascular morbidity during a 10-year follow-up ⁽¹²³⁾.

Among old-line diabetes medications, metformin has been considered, over decades, to possess the best properties to reduce diabetes-related endpoints. In a sub-study of the United Kingdom Prospective Diabetes Study, glucose control with metformin proved to be more effective in reducing the risk of diabetes-related complications than sulfonylurea or insulin among overweight diabetics. Compared to the dietary treatment group, the metformin group had a 32% lower risk for diabetes-related endpoints, while the corresponding risk reduction in the sulfonylurea or insulin group was 7%. For all-cause mortality, the risk reduction was 36% in the metformin group and 8% in the sulfonylurea or insulin group, respectively. The risk reduction of myocardial infarction was 39% in the metformin group and 21% in the sulfonylurea or insulin group, respectively ⁽¹²⁴⁾.

Novel blood-glucose-lowering medications, such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists, have been shown to reduce the risk of major adverse cardiac events ⁽¹²⁵⁾. According to a meta-analysis with 351,476 diabetics, SGLT-2 inhibitors significantly reduced all-cause mortality, cardiovascular mortality and non-fatal myocardial infarction with hazard ratios of 0.67 (95% CI, 0.54 to 0.84), 0.77 (95% CI, 0.60–0.98) and 0.86 (95% CI, 0.76–0.98), respectively ⁽¹²⁶⁾. In a study using network meta-analysis, the authors reported the clinical efficacy of SGLT-2 inhibitors, GLP-1 agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors in the treatment of type 2 diabetes. Compared to the controls, the hazard ratio for cardiovascular mortality was 0.79 (95% credible intervals {CrI}, 0.69 to 0.91) for SGLT-2 inhibitors, 0.85(95% CrI, 0.77 to 0.94) for GLP-1 agonists and 1.0 (95% CrI, 0.91 to 1.11) for DPP-4 inhibitors. The corresponding absolute risk difference (RD) was -0.8 (95% CrI, -1.1 to -0.3) for SGLT-2 inhibitors, -0.5(95% CrI, -0.8 to -0.1) for GLP-1 agonists and 0.0 (95% CrI, -0.3 to 0.4) for DPP-4 inhibitors, respectively. The hazard ratios for all-cause mortality were comparable to the hazard ratios for cardiovascular mortality with all three medications ⁽¹²⁷⁾. Moreover, SGLT-2 inhibitors have shown to improve cardiac function, providing additional benefits to diabetics experiencing heart failure ⁽¹²⁸⁾.

4.6 Overall cardiovascular risk

Historically, cardiovascular (CV) risk has been assessed based on a single risk factor. The understanding that several interacting risk factors determine atherosclerotic CVD led to the introduction of the concept of ‘total CV risk’.

In 1991, based on the Framingham study cohort of 5,573 subjects (53.5% women), a risk function was published to assess five- and 10-year risk for CHD. The following risk factors were considered in the risk function: age, sex, systolic and diastolic BP, total cholesterol, HDL-cholesterol, diabetes, smoking status and left ventricular hypertrophy based on ECG findings ⁽¹²⁹⁾. Subsequently, several modified versions of the Framingham risk function have been published, including a version where left ventricular hypertrophy is omitted and LDL-cholesterol is optionally added for use instead of total cholesterol ⁽¹³⁰⁾. In 1994, the first ‘European recommendations on the prevention of coronary heart disease in clinical practice’ were introduced. The recommendations were comprised of a coronary

risk chart to assess the absolute 10-year risk for CHD. The risk function and the chart based on the risk function were derived from the above-mentioned Framingham Study, but fewer risk factors were included, that is age, sex, SBP, total cholesterol and smoking ⁽¹³¹⁾. A year before the European recommendations, the National Advisory Committee on Core Health and Disability Support Services, New Zealand, published recommendations according to which the treatment of raised BP should be based on the absolute risk of CVD rather than on BP alone ⁽¹³²⁾.

The European Recommendations on the Prevention of Coronary Heart Disease in Clinical Practice were updated in 1998. The updated recommendations considered the accumulated new scientific evidence of lifestyle guidance and medication to achieve risk factor goals. However, the CHD risk-estimating chart remained unchanged ⁽¹³³⁾. The Systematic Coronary Risk Evaluation (SCORE) Project was initiated in 1994 as a joint venture between the European Societies of Cardiology and Hypertension and the European Atherosclerosis Society. A European scoring method was deemed necessary due to shortcomings with the use of risk scoring based on the Framingham study from the U.S. The Framingham scoring method was based on a rather small population (5,573 people), and it overestimated the risk of cardiovascular events in some European populations. Furthermore, the end point was morbidity and mortality from CHD, not total cardiovascular mortality as in the SCORE project ⁽¹³⁴⁾. ‘Estimation of Ten-Year Risk of Fatal CVD in Europe: The SCORE Project’ was published in 2003. It was based on 12 pooled prospective studies from 11 European countries, including 205,178 people (88,080 women and 117,098 men) representing 2.7 million person years of follow-up and 7,934 documented cardiovascular deaths. The SCORE model, based on this data, estimates the absolute 10-year risk of a first fatal cardiovascular event, including all International Classification of Disease codes that can be considered to be atherosclerotic. The built-up risk equation was a function of age, gender, SBP, total cholesterol or total cholesterol and HDL-cholesterol ratio, and smoking status. Two SCORE risk charts were compiled, one for high-risk and one for low-risk regions of Europe. Both regional charts had parallel charts, one with total cholesterol and the other with total and HDL-cholesterol ratio as lipid variables. The SCORE model is intended for risk stratification in the primary prevention of CVD ^(135, 136). The latest version of ‘European Guidelines on CVD Prevention in Clinical Practice’ was published in 2016 ⁽³⁾. The European Guidelines categorise CVD risk on four levels: very high-risk, a calculated SCORE $\geq 10\%$; high-risk, a calculated

SCORE $\geq 5\%$ but $< 10\%$; moderate risk, a calculated SCORE $\geq 1\%$ but $< 5\%$; and low-risk, a calculated SCORE $< 1\%$. The recommendation follows the principle that the higher the risk, the more intense the treatment approach should be. To guide preventive measures, the latest guidelines equate the following situations with a very high risk: documented CVD, DM with target organ damage such as proteinuria or with a major risk factor, severe chronic kidney disease (CKD) – that is GFR < 30 ml/min/1.73 m², with a high risk: DM (with the exception of young people with type 1 DM without major risk factors) and those with moderate CKD - that is a GFR 30–59 ml/min/1.73 m² ⁽³⁾.

There are substantial differences between European countries regarding CVD deaths ⁽¹³⁷⁾. Relatively high age-standardised death rates can be identified in Eastern and Central Europe, while the rates are lower in Northern, Western and Southern Europe ⁽¹³⁸⁾.

The SCORE model has the advantage that it can be recalibrated at the national level. Recalibration requires recent and precise estimates of mortality and risk factor statistics. Recalibrated country-specific versions of the SCORE model exist for 17 European countries. Based on SCORE risk charts, a web-based calculator called HeartScore was produced. HeartScore includes versions of high- and low-risk countries, total cholesterol and the total cholesterol/HDL-cholesterol ratio ⁽¹³⁹⁾.

Since 2008, it has been possible to estimate the 10-year risk for CHD, stroke and their combination by Finland's calculator, FINRISK ⁽¹⁴⁰⁾. The model is based on a 10-year follow-up of a random population sample of 19,447 citizens (52% women) from three cohorts in 1982, 1987 and 1992 of the FINRISK survey. The model estimates a 10-year risk for CHD, stroke and their combination. The risk is predicted by sex, age, smoking, SBP, total cholesterol, HDL-cholesterol, diabetes and family history of CVD ⁽¹⁴¹⁾.

Other models have been developed to stratify the asymptomatic population on the basis of total CV risk into the subgroups of low, moderate, high and very high risk. Most models are based on major CV risk factors, that is age, gender, smoking, BP and lipids. A few other risk factors have been included in commonly used models (Table 2). Over the last decade, researchers have attempted to discern whether adding novel biomarkers to existing models will improve the total CV risk estimation.

It can be concluded from the literature that, in estimating the total CV risk of an asymptomatic person, traditional cardiovascular risk factors explain most of an individual's risk. Adding novel biomarkers from the fields of inflammation, coagulation or subclinical vascular damages has only modest and inconsistent effects on existing models ⁽¹⁴²⁾. Therefore, their usage should be limited to subjects with the therapeutic dilemma of an intermediate total CV risk ^(143, 144).

Table 2. Commonly used total CV risk estimation models

Model	Based on data from	Sample size	Estimate	Variables	Comments
Framingham (145)	Framingham Heart and offspring studies Massachusetts, USA	4,522 women and 3,969 men	10-year risk of CHD events, latest version 10-year risk of CVD events	Sex, age, total cholesterol, HDL-C, SBP, smoking, DM, hypertensive treatment	In version, BMI has replaced lipid measurements
Score (3)	12 prospective studies from 11 European countries	88,080 women and 117,098 men	10-year CVD mortality risk	Sex, age, total cholesterol, or total cholesterol to HDL- C ratio, SBP, smoking	Versions for use in low- and high-risk countries
Assign-score (146)	SHHEC prospective study Scotland	6,757 women and 6,540 men	10-year CVD risk	Sex, age, total cholesterol, HDL-C, SBP, smoking, DM, FH of CVD	Variables include area- based index of deprivation
QRISK2 (147)	QRESEARCH database England and Wales	2.29 million individuals	10-year CVD risk and lifetime risk of CVD events	Sex, age, total cholesterol to HDL- C ratio, SBP, smoking, DM, BMI, BP treatment, ethnicity	Variables also included area-based index of deprivation

PROCAM (148)	The Prospective cardiovascular Münster (PROCAM) study Germany	5,389 men	10-year risk of major coronary and cerebral ischaemic events	Sex, age, LDL-C, HDL-C, TG, SBP, DM, FH of CVD, smoking	Recent change in methods allows extension of risk estimation to women
Pooled Cohort Equations (149)	4 pooled prospective studies: ARIC, CHS, CARDIA, Framingham (original and offspring studies) USA	11,240 white women and 9,098 men; 2,641 African American women and 1,647 men	10-year risk for a first atherosclerotic CVD event lifetime risk	Sex, age, race (white or other/African American), total cholesterol, HDL-C, SBP, antihypertensive medication, DM, smoking	Recommended by AHA/ACC Guidelines on the Assessment of CVD Risk
GLOBORISK (150)	8 North American prospective studies	16,806 women and 33,323 men	10-year risk of fatal CVD	Sex, age, total cholesterol, SBP, DM	Equation can be recalibrated

BMI = body mass index, BP = blood pressure, CHD = coronary heart disease, CVD = cardiovascular disease, DM = diabetes mellitus, FH = family history, HDL-C = high-density cholesterol, LDL-C = low-density cholesterol, SBP = systolic blood pressure, TG = triglycerides

4.7 Risk screening and health counselling

‘There should be no screening without adequate resources for advice and long-term care’, on page 70 of *The Strategy of Preventive Medicine*, by Geoffrey Rose (1992)

A one-year follow-up study included 100 men and women (64% women) with a mean age of 56 (± 10) years. The inclusion criterion of the study was at least three of the following cardiovascular risk factors: physical inactivity, unhealthy eating habits, smoking, risky consumption of alcohol, high prolonged stress, overweight, abdominal obesity, dyslipidaemia, high BP, insulin resistance, diabetes or previous CVD. The study's process included a health check-up, risk assessments and lifestyle counselling at baseline, at six months and at one year. Between the baseline and six-month visits, there were five group sessions. During the one-year study period, the change in proportions of high SBP was from 49% to 30% and in DBP from 38% to 19%, respectively. Systolic BP decreased from 135 mmHg at baseline to 130 mmHg at the one-year visit, and mean DBP decreased from 85 mmHg to 80 mmHg. A decreasing trend of systolic and diastolic BP was found among participants with and without BP-lowering medication. WC decreased over the study period from 108.4 cm to 105.9 cm. TC concentrations decreased from 5.1 mmol/l at baseline to 4.9 mmol/l at the six-month visit. No further change was seen at the one-year visit. A similar trend was reported in LDL-cholesterol. The overall cardiovascular risk according to the Framingham 10-year predicting model decreased significantly from the baseline (15.6%) to the one-year follow-up (13.3%) in the total study population. At the baseline, the overall cardiovascular risk was 23.5% in men and 10.8% in women, respectively. At the one-year visit, the corresponding numbers were 18.4% for men and 8.6% for women. The risk reduction over the one-year period was practically the same for men and women – 21.7% and 20.3%, respectively. The risk reduction was 21% among those with CVD and 28% among those without CVD ¹⁵¹.

A systematic review of 74 trials targeted healthy lifestyle counselling for individuals with cardiovascular risk factors, of which 49 trials evaluated combined lifestyle counselling (healthy diet and physical activity) interventions, 18 diet-only

interventions and 10 physical activity-only interventions. At the 12- to 24-month follow-up, combined lifestyle counselling intervention trials reported decreased total cholesterol and LDL-cholesterol levels, BP, fasting glucose levels, diabetes incidence and weight. Diet-only counselling also reduced total cholesterol and LDL cholesterol levels. The authors did not find consistent evidence of benefits for cardiovascular risk factors from evaluated physical activity-only trials ¹⁵².

In another study, 168 middle-aged men with at least two cardiovascular risk factors who were physically inactive (physical activity < 3 times per week) were divided into three groups: lifestyle counselling, lifestyle counselling plus three months of weekly group exercise intervention and a control group. At the one-year follow-up visit, the total proportion of physically active participants (PA \geq 3 times per week) was 19%. Viewed by group, in the lifestyle counselling-only group, the physically active proportion was 16%, in the lifestyle counselling plus exercise intervention 26% and in the control group 17%, respectively. The results did not show meaningful impact on any other cardiovascular risk factors ¹⁵³. Another study including the same population as above reported significant improvements in self-rated health and self-rated wellbeing across all groups. Moreover, the proportion of depressive participants, assessed by the Patient Health Questionnaire-2, decreased in two intervention groups but not among the controls during the one-year study period. The participants with a depressive score \geq 3 decreased from 27% to 13% in the group receiving lifestyle counselling only, lessened from 34% to 18% in the group receiving lifestyle counselling plus exercise intervention and increased from 26% to 31% in the control group ¹⁵⁴.

The current practice has brought a new approach to cardiovascular risk management. In a systematic review and meta-analysis, a total of 57 studies (n = 19,862) evaluated the impact of Web-based intervention on cardiovascular risk factor management to reduce the risk of CVD in older people. In a subgroup analysis of eight studies (n = 2,321) targeting overall cardiovascular risk scores, a small but significant improvement was detected during the follow-up in risk score value – that is a weighted standardised mean difference of -0.10 (95% CI -0.18 to -0.02; $I^2=0\%$) ¹⁵⁵. A web-based health risk assessment study with tailored feedback regarding individual health promotion evaluated the effects on the lifestyles of employees at a Dutch worksite. Their mean age was 45 years. Gender was not reported. The mean follow-up time was 15 months. Positive changes were detected only in physical activity, as the proportion of those who performed physical activity \geq 150 min per week increased from 46% at the baseline to 71% at the

follow-up. No difference was seen in the proportions meeting the recommendations for the daily intake of fruit and vegetables, moderate alcohol consumption and smoking cessation ¹⁵⁶.

Several on-line applications are available for health checks and counselling. One is the Virtual Health Check and Personal Coaching programme developed by the Finnish Medical Association Duodecim. The virtual health check provides users with information about risk factors aimed at improving their health. Based on risk profile, the programme estimates life expectancy and disease risk. A registered user can start an eight- to 12-week coaching programme that provides regular feedback. The Virtual Health Check and Personal Coaching application is available at https://starscience.duodecim.fi/star_de.

5 AIMS OF THE STUDY

In this series of studies, we investigated the relationship between central obesity and cardiovascular risk factors and evaluated the long-term effect of lifestyle counselling on cardiovascular risk factors in middle-aged men.

The aims of the studies were:

1. To assess the predictive value of a single anthropometric measure, WC, as a cardiovascular risk indicator (study I).
2. To explore the associations between abdominal fat deposits and cardiovascular risk factors in abdominally obese middle-aged men (study II).
3. To evaluate the impact of lifestyle counselling based upon personal cardiovascular risk estimation during a two-year follow-up considering individual socioeconomic status (study III).
4. To evaluate the long-term influence of risk assessment and lifestyle counselling on lifestyle, cardiovascular risk factors and total cardiovascular risk considering the continuation of risk communication without a preconceived plan (study IV).

6 METHODS

6.1 Subjects

6.1.1 Study I

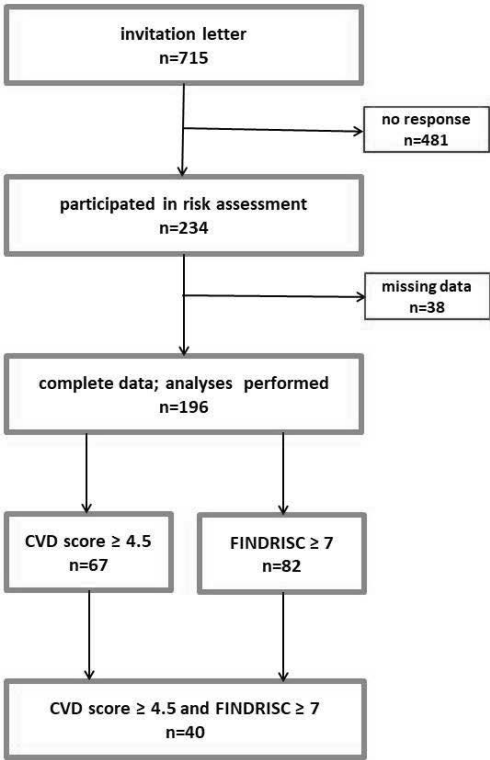


Figure 3. Flow chart of Study I

The Health Centre of the City of Helsinki and the Helsinki Heart District conducted a study called the MBO project between 2001 and 2005 ⁽¹⁵⁷⁾. The study’s population consisted of men aged 40, 45, 50 and 55 living in the north-eastern part of Helsinki. The study was intended to develop a method by which to identify

cardiometabolic risk factors among middle-aged men, to make them aware of their risks and to encourage risk management. At a risk assessment visit in the Helsinki Heart District with a public health nurse, men with an elevated risk were given lifestyle counselling and were invited to a follow-up visit within six months' time.

The present study deals with data from the youngest (men age 40) cohort of the MBO project collected at the first visits in 2001. The potential study population comprised 715 invitations to men aged 40. Of these men, 234 responded and participated in the risk assessment visits. Due to the lack of data from 38 subjects, 196 subjects were included in the final analyses (Figure 3).

6.1.2 Study II

This part of the thesis deals with the original study 2 only to the extent that it describes the associations between abdominal obesity and CV risk factors.

Through advertisements in local newspapers, 77 middle-aged men were recruited to the study. The participants had to meet the following criteria: no known acute or chronic disease based upon history, physical examination or a standard laboratory test (diabetes or its absence was confirmed by a 2-h oral glucose tolerance test) and an alcohol consumption of ≤ 20 g per day. Participants were allocated into two groups with or without metabolic syndrome (Mets), based on the harmonised criterion of MetS⁽¹⁵⁸⁾. Thirty-seven participants out of 77 fulfilled the criterion for the MetS.

6.1.3 Studies III and IV

Since 2006, the City of Helsinki has provided a systematic cardiometabolic risk assessment including a lifestyle interview and counselling for all men aged 40 living in Helsinki. Initially, these activities were launched with the Helsinki Heart District, a member of the Finnish Heart Association. The latter was the initiating party and was responsible for training the study's nurses and developing the tools used for guidance. Of the 4,274 men originally invited to the risk assessment visit in 2006, 1,454 (34%) participated. Out of these, 471 men were found with an elevated CV risk assessed with a modified North-Karelia project risk tool⁽¹⁵⁹⁾. All men with an elevated CV risk received lifestyle counselling based on their

individual risk profile according to current guidelines for preventing CVD, which was in line with European guidelines on CVD prevention in clinical practice ⁽¹³³⁾. The 60-minute-long session (lifestyle interview and counselling) with a public health nurse was supplemented with printed health education materials addressing physical activity, smoking cessation and dietary habits. The educational material was produced by the Finnish Heart Association and the Finnish Diabetes Association. The lifestyle interview included questions about types of fat used for bread spreads and for cooking. The alternatives were vegetable margarine, vegetable oil and butter. Information about leisure-time physical activities and smoking habits was collected by a questionnaire (Appendix 2). All men with an elevated risk were advised to be in contact with healthcare providers for CV-risk monitoring every one to two years. Future visits depended on the men's own motivation, without any preconceived plan. They were to choose their own service provider, that is their local healthcare centre for normal day-to-day practice, occupational health services or private healthcare services. According to the study plan, all participants would be invited to attend follow-up visits after two and five years. Those who took part in a two-year visit in 2008 and a five-year visit in 2011 gave their written informed consent for their participation at that visit.

Table 3. Modified cardiovascular risk score of the North Karelia project

Score	BMI kg/m ²	Current smoking	Physical activity ^a	Systolic BP mmHg	Diastolic BP mmHg	Cholesterol mmol/l
0	≤ 24.9	0	≥ 3x/week	≤ 129	≤ 79	≤ 4.9
0.5	25– 26.9	Occasionally	1–2x/week	130–139	80–89	5.0–5.4
1.0	27– 28.9	1–4/day	Approx. 1x/week	140–149	90–94	5.5–5.9
1.5	29– 30.9	5–9	Sometimes	150–159	95–99	6.0–6.4
2.0	≥ 31	10–14	Never	≥ 160	≥ 100	6.5–6.9
2.5	–	15–19	–	–	–	7.0–7.4
3.0	–	20–24	–	–	–	7.5–7.9
3.5	–	25–29	–	–	–	8.0–8.4
4.0	–	30	–	–	–	≥ 8.5

BMI = body mass index, BP = blood pressure and TC = total cholesterol. ^a Continuous physical exercise (duration at least 30 min) causing sweating or shortness of breath. According to the criteria used, high-risk persons have a risk score of ≥ 4.5 (sum of scores).

6.2 Measurements and examination

6.2.1 Studies I, III and IV

At the screening visit, detailed information on leisure time physical activity (LTPA), smoking habits, use of alcohol and family history of CVD and diabetes,

among others, was obtained from a self-administered questionnaire (appendices 1 and 2) which was completed by a nurse at the examination. In addition, dietary habits were assessed. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg in light indoor clothing without shoes. BMI was calculated as kg/m^2 . WC was measured once in a standing position midway between the lowest rib and the iliac crest. Blood pressure was measured with the subject in a sitting position using an automated sphygmomanometer (Omron HEM-7051-E, Kyoto, Japan). The mean of two successive readings was recorded. All measurements were made in accordance with standard techniques. Blood samples were drawn by a trained technician after an overnight fast and analysed for lipids and glucose in a certified central laboratory. CVD risk was assessed using a modified version of the North-Karelia project risk chart (Table 3 and Appendix 2) which is based on BMI, smoking status, leisure-time physical activity, systolic and diastolic BP and total cholesterol concentration ^(152,160). The risk score can range from zero to 16. Subjects with a risk score ≥ 4.5 are considered to have an elevated risk for CVD. The Finnish Diabetes Risk Score (FINDRISC) (appendix 1) was used to assess the risk for type 2 diabetes ⁽¹⁶¹⁾.

6.2.2 Study II

WC was measured once in a standing position midway between the iliac crest and the lowest rib margin. BMI was calculated as kg/m^2 . Blood pressure was measured by BPM-200 (Quick Medical, Snoqualmie, Washington) in the sitting position after a five-minute rest, and the mean of five measurements was recorded. Blood samples were drawn after overnight fasting. Total serum cholesterol, TG, very low-density lipoprotein cholesterol (VLDL-1) TG, HDL-C, free fatty acids, apolipoprotein A-I, apolipoprotein B and high-sensitivity C-reactive protein (CRP) were measured by an autoanalyzer. The concentration of low-density lipoprotein cholesterol was calculated using the Friedewald formula ⁽¹⁶²⁾. Fasting glucose and standard two-hour 75 g oral glucose tolerance tests were performed; plasma glucose was assessed using the hexokinase method. Insulin concentration was determined by a two-site immunoradiometric assay. The insulin-resistance homeostasis model assessment (HOMA) index was calculated using the formula: $(\text{fasting plasma glucose} \times \text{fasting plasma insulin})/22.5$ ⁽¹⁶³⁾. Smoking status was recorded as present, past or non-smoker.

Hepatic TG content, distribution and volumes of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were measured with a whole-body magnetic resonance (MR) imager. The VAT/SAT ratio was calculated as a metric of abdominal fat distribution.

6.2.3 Study III follow-up

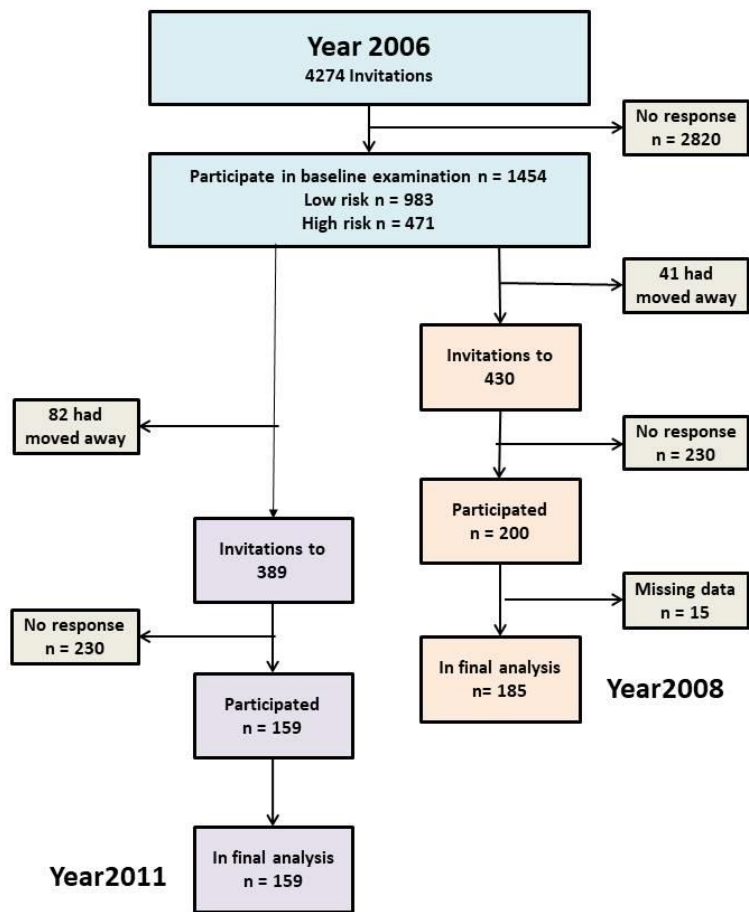


Figure 4. Flow chart of studies III and IV

Of the men with an elevated risk ($n = 471$) at the screening visit in 2006, a total of 430 were identified from the local healthcare centre register in 2008 and were invited to a follow-up visit. Of these, 200 (47%) participated. Information on educational attainment was available for 185 (93%) of the men (Figure 4). The subjects experienced the same examinations and were interviewed about lifestyles in a similar way as at the screening visit. Since the collected data enabled CV-risk assessment while applying the Framingham equation for primary healthcare ⁽¹⁴⁵⁾, this CVD assessment was included in the study. To determine the impact of socioeconomic status (SES) on CV-risk factors during the two-year follow-up period, we categorised men into three levels according to their educational attainment (low ≤ 9 years, middle 10 to 12 years and high ≥ 13 years).

6.2.4 Study IV follow-up

In 2011, a total of 389 men who originally had an elevated CV risk were identified from the local healthcare centre register and were invited for a re-evaluation visit. Of these, 159 (41%) participated (Figure 4). These men underwent the same examinations and were interviewed for lifestyles in a similar way as at the screening visit. In addition, their CV risk was assessed with the SCORE Chart ⁽³⁾. Information was collected about fulfilled contacts with healthcare providers for CV-risk monitoring after the baseline screening visit. Contacts with the public healthcare centre were checked from the medical records of the participants, but information on contacts with occupational healthcare was based on participants' own reports.

6.3 Statistical methods

6.3.1 Study I

Calculations of sensitivity, specificity and predictive values of 11 cut-off points for WC (92 cm through 102 cm) were based on a 2 x 2 contingency table, where WC was used as the independent variable and the risk status as the dependent variable. The former calculation was performed with the Confidence Interval Analysis (CIA), for Windows version 2.1.2 software according to Wilson's method. The receiver operating characteristic (ROC) curve was constructed with SPSS statistics using WC as the test variable and the risk status as the state variable.

6.3.2 Study II

The distribution of continuous variables was analysed by the Kolmogorov-Smirnov test. Data were presented as means with standard deviations for normally distributed variables, as medians in the 0.25–0.75 interquartile range for skewed variables and as percentages for categorical variables. The Mann-Whitney *U* test, unpaired *t* test and χ^2 test were applied, as appropriate, to assess between-group differences. Correlation analyses were adjusted for age and smoking status. Univariate regression analyses were performed to detect determinants of hepatic TG content, visceral fat and VAT/SAT ratio. Stepwise multivariable linear regression analyses were used to evaluate the impact of fat deposits on cardiometabolic risk factors as dependent variables

6.3.3 Studies III and IV

The data are presented for continuous variables as means with standard deviations and categorical variables as percentages. The 95% confidence intervals are given for differences of the means. The comparison of continuous variables within one group (between baseline and follow-up visits) was performed with paired *t*-tests. The one-way ANOVA was performed to determine distinctions in continuous variables between the groups. Within-group changes in continuous variables were compared between the groups with the Univariate General Linear model.

The comparisons of categorical variables within one group (between baseline and follow-up visits) were performed with Wilson's method for paired samples' proportions and their distinctions using Confidence Intervals Analysis (CIA) software for Windows. The differences of categorical variables between the groups were analysed by Freeman-Halton extension of Fisher's exact test ⁽¹⁶⁴⁾. Within-group changes in categorical variables were compared between the groups with the Binary Logistic Regression model.

Unless otherwise stated, the statistical software used was: study I, SPSS 16.0 for Windows (SPSS Inc., Chicago IL, USA); study II, SPSS 19.0 for Windows (SPSS, Inc., Chicago, Illinois, USA); study III, SPSS 18.0 for Windows (SPSS INC., Chicago IL, USA); and study IV, SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

6.4 Ethical considerations

The Helsinki University Central Hospital Ethics Committee approved the protocol of all studies, and in all studies, subjects provided their written informed consent.

7 RESULTS

7.1 Study I

Of the 715 invited men, 234 (32.7%) participated in the risk assessment visits at Helsinki heart district. At the beginning of recruitment in 2001, the FINDRISC chart was unavailable. Therefore, the assessment of FINDRISC was missing from 38 men. Sufficient data for analyses were available from 196 men. In 87 participants, neither of the risk scores (CVD risk score or FINDRISC score) was elevated; at least one of the risk scores was raised in 109 men. Among these, 67 had a CVD risk score ≥ 4.5 , and 82 had a FINDRISC ≥ 7 . Both risk scores were elevated in 40 participants. Table 4 shows the characteristics of the participants grouped according to risk status. The variation in individual risk factors is at its highest 20% between the low-risk and the elevated risk groups. Notably, those with elevated risk have two to three times higher RR for CVD and type 2 diabetes compared with low-risk participants.

Table 4. Characteristics of the participants according to risk status

	CVD risk < 4.5 and FINDRISC < 7 n = 87	CVD risk ≥ 4.5 n = 67	FINDRISC ≥ 7 n = 82
BMI kg/m ²	23.9 (2.5)	28.3 (4.0)	28.9 (3.7)
WC cm	90.0 (6.4)	102.3 (10.5)	104.1 (10.0)
SBP mmHg	125 (13.1)	139 (16.9)	134 (14.8)
DBP mmHg	82 (8.1)	93 (9.9)	89 (9.2)
Total-C mmol/l	4.54 (0.79)	6.00 (0.97)	5.28 (1.07)
LDL-C mmol/l	2.45 (0.93)	3.95 (0.92)	3.24 (1.06)
HDL-C mmol/l	1.67 (0.46)	1.29 (0.36)	1.32 (0.40)
TG mmol/l	1.58 (0.46)	1.69 (0.77)	1.84 (0.88)
Glucose mmol/l	5.37 (0.74)	5.45 (0.54)	5.38 (0.53)
FINDRISC	3.1 (2.0)	7.5 (3.6)	9.2 (2.4)
CVD risk score	2.0 (1.2)	6.8 (1.8)	4.8 (2.7)

Data are means and (SD). BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, Total-C = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides.

Table 5. Sensitivity, specificity and positive and negative predictive value of WC as a diagnostic test for the elevated risk of CVD disease and type 2 diabetes

WC cm	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
92	0.88 (0.81 to 0.93)	0.62 (0.52 to 0.72)	0.74 (0.63 to 0.81)	0.81 (0.70 to 0.88)
93	0.85 (0.78 to 0.91)	0.69 (0.59 to 0.78)	0.78 (0.69 to 0.84)	0.79 (0.69 to 0.87)
94	0.84 (0.76 to 0.90)	0.78 (0.68 to 0.86)	0.83 (0.75 to 0.89)	0.80 (0.70 to 0.87)
95	0.80 (0.71 to 0.86)	0.82 (0.72 to 0.88)	0.85 (0.76 to 0.90)	0.76 (0.67 to 0.84)
96	0.74 (0.65 to 0.82)	0.83 (0.74 to 0.89)	0.84 (0.76 to 0.90)	0.72 (0.63 to 0.80)
97	0.65 (0.56 to 0.73)	0.85 (0.76 to 0.91)	0.85 (0.75 to 0.91)	0.66 (0.57 to 0.74)
98	0.64 (0.55 to 0.73)	0.89 (0.80 to 0.94)	0.88 (0.79 to 0.93)	0.66 (0.57 to 0.74)
99	0.58 (0.48 to 0.67)	0.91 (0.83 to 0.95)	0.89 (0.79 to 0.94)	0.63 (0.55 to 0.71)
100	0.53 (0.44 to 0.62)	0.91 (0.83 to 0.95)	0.88 (0.78 to 0.94)	0.61 (0.52 to 0.69)
101	0.47 (0.38 to 0.56)	0.95 (0.89 to 0.98)	0.93 (0.83 to 0.97)	0.59 (0.51 to 0.67)
102	0.41 (0.33 to 0.51)	0.97 (0.91 to 0.99)	0.94 (0.83 to 0.98)	0.57 (0.49 to 0.65)

WC = waist circumference, PPV = positive predictive value, NPV = negative predictive value and (95% CI) = 95% confidence interval

Besides the values depicted in Table 5 the calculations indicate that a $WC \geq 94$ cm has the best accuracy from the selected cut-off points to differentiate those with no elevated risk scores from those with at least one of the two elevated risk scores. For example, for a $WC \geq 93$ cm, the accuracy is $156/196 = 0.781$; for a WC of ≥ 94 cm, $160/196 = 0.816$; and for a WC of ≥ 95 cm, $158/196 = 0.806$, respectively. In the equation, numerators are the sum of true positive and true negative proportions, and the denominator is the number of the tested population.

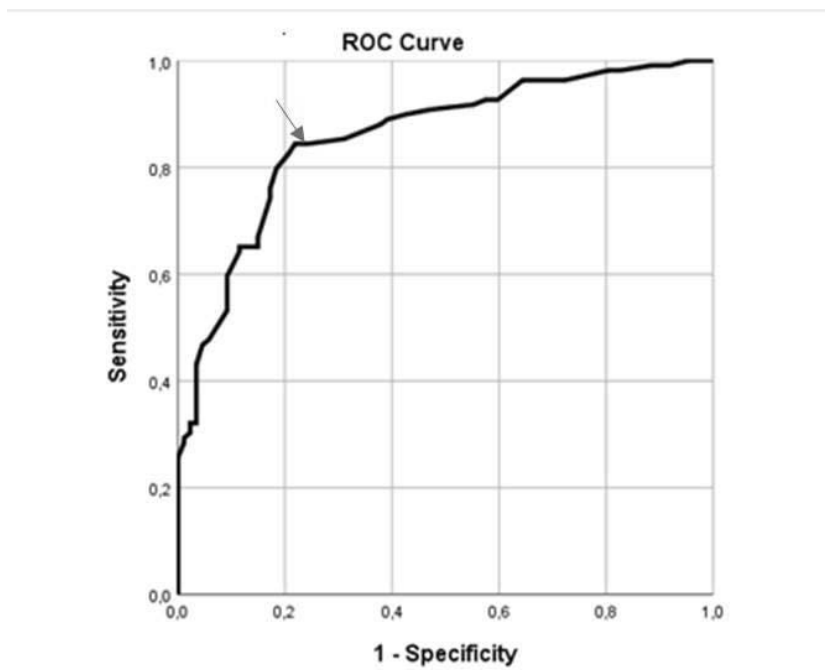


Figure 5. The receiver operating characteristic curve. The arrow on the curve corresponding waist circumference of ≥ 94 cm with coordinates; sensitivity = 0.844 and 1-specificity = 1 - 0.782.

In Figure 5, the area under the curve is 0.858 (95% CI; 0.805 to 0.910). The area under the curve decreases when the cut-off of the FINDRISC score is raised from 7 to 9 and further to 12. The corresponding area under the curve is as follows: 0.773 (95% CI 0.707 to 0.831) and 0.761 (95% CI 0.690 to 0.831).

7.2 Study II

Clinical and biochemical characteristics of the study's subjects are summarised in Table 6. In all of the parameters presented, the difference between the groups was statistically significant. All participants without MetS had normal glucose tolerance, whereas in the MetS group, four participants had impaired fasting glucose, and nine, impaired glucose tolerance. Subjects with a high level of intra-abdominal fat presented characteristics of MetS, elevated WC, triglycerides, insulin

resistance, BP and decreased HDL-cholesterol compared to subjects with a low level of intra-abdominal fat. They were also overall older, with higher BMI and pronounced smoking habits compared to subjects with lower levels of intra-abdominal fat. The difference between the groups in the amount of visceral fat was considerable, being 3.9 times higher in the MetS group than those without MetS.

Table 6. Characteristics of the study's groups

	MetS present	MetS absent	P values
N (men)	37	40	
Age, y	47 (6)	40 (8)	< 0.001
Current smoker, n (%)	13 (35)	5 (12)	0.019
WC, cm	107.0 (94.0–135.0)	87.0 (71.0–93.5)	< 0.001
BMI, kg/m ²	30.9 (24.2–42.5)	23.4 (17.6–29.8)	< 0.001
Systolic BP, mmHg	132 (14)	115 (10)	< 0.001
Diastolic BP, mmHg	88 (9)	74 (6)	< 0.001
Total cholesterol, mmol/l	5.25 (0.74)	4.41 (0.79)	< 0.001
LDL-cholesterol, mmol/l	3.25 (0.71)	2.54 (0.66)	< 0.001
HDL-cholesterol, mmol/l	1.02 (0.26)	1.50 (0.39)	< 0.001
TG, mmol/l	2.20 (0.65–6.26)	0.78 (0.35–1.57)	< 0.001
fP-glucose, mmol/l	5.8 (4.6–6.9)	5.0 (4.4–6.0)	< 0.001
fS-insulin, mU/l	9.3 (3.3–36.9)	2.9 (0.9–7.7)	< 0.001
HOMA index	2.6 (0.8–8.0)	0.6 (0.2–2.0)	< 0.001
High-sensitivity CRP, mg/l	1.8 (0.2–11.8)	0.2 (0.0–5.8)	< 0.001
Hepatic TG content, %	6.59 (0.40–31.74)	0.73 (0.17–4.45)	< 0.001
Visceral fat, cm ³	3304(1257– 5743)	843 (67–3170)	< 0.001
Subcutaneous fat, cm ³	4816(2216– 9354)	1773 (284–4017)	< 0.001
VAT/SAT ratio	0.63 (0.26–1.64)	0.46 (0.13–1.23)	< 0.001

fS = fasting serum, fP = fasting plasma, TG = triglycerides, HOMA = homeostatic model assessment, CRP = c-reactive protein, VAT = visceral adipose tissue and SAT = subcutaneous adipose tissue. P values are for the difference between two groups. Data are presented as means (SD), median (range) or (%).

In an association analysis presented in Table 7 visceral fat and hepatic TG content showed statistically significant positive correlations with WC, BMI, systolic and diastolic BP, triglycerides, fasting plasma glucose, fasting plasma insulin, HOMA index, subcutaneous fat and VAT/SAT ratio, whereas the correlation with HDL-cholesterol was negative. A statistically significant, but weaker, correlation was found between VAT/SAT ratio and hepatic TG content.

Table 7. Univariate correlation coefficients between hepatic TG content, visceral fat, VAT/SAT ratio and cardiometabolic risk factors. Adjusted for age and smoking.

	Hepatic TG content	Visceral fat	VAT/SAT ratio
Age	0.221	0.416 ^c	0.510 ^c
WC	0.607 ^c	0.842 ^c	0.129
BMI	0.584 ^c	0.807 ^c	0.063
Systolic BP	0.308 ^b	0.401 ^c	0.087
Diastolic BP	0.413 ^c	0.493 ^c	0.118
Total cholesterol	0.037	0.146	0.091
LDL cholesterol	0.051	0.211	0.162
HDL cholesterol	- 0.321 ^b	- 0.590 ^c	- 0.286 ^a
TG	0.254 ^a	0.486 ^c	0.183
Fasting plasma glucose	0.369 ^b	0.445 ^c	0.143
Fasting serum insulin	0.508 ^c	0.648 ^c	0.213
HOMA index	0.536 ^c	0.761 ^c	0.228 ^a
High-sensitivity CRP	0.229	0.373 ^b	- 0.110
Hepatic TG content	—	0.779 ^c	0.477 ^c
Visceral fat	0.779 ^c	—	0.537 ^c
Subcutaneous fat	0.514 ^c	0.764 ^c	- 0.028
VAT/SAT ratio	0.476 ^c	0.537 ^c	—

^a p < 0.05; ^b p < 0.01; ^c p < 0.001

In stepwise multivariable regression analyses, visceral fat proved to be an independent determinant of triglycerides, HDL-cholesterol, plasma glucose, serum insulin and HOMA index. Age and subcutaneous fat were independent predictors of systolic and diastolic BP; see Table 8.

Table 8. Stepwise multivariable regression analyses

Dependent variable	Independent variable	β	p-value
Triglycerides (log)	Age	- 0.107	0.252
	Hepatic TG t (log)	- 0.203	0.215
	Visceral fat (log)	- 0.654	< 0.001
	Subcutaneous fat (log)	- 0.265	0.097
	Adjusted R ²	0.488	< 0.001
HDL cholesterol	Age	0.242	0.021
	Hepatic TG (log)	0.268	0.141
	Visceral fat (log)	- 0.686	< 0.001
	Subcutaneous fat (log)	- 0.098	0.584
	Adjusted R ²	0.364	< 0.001

Fasting glucose (log)	Age	0.030	0.777
	Hepatic TG (log)	0.170	0.373
	Visceral fat (log)	0.411	0.002
	Subcutaneous fat (log)	0.215	0.238
	Adjusted R ²	0.345	< 0.001
Fasting insulin (log)	Age	- 0.009	0.892
	Hepatic TG (log)	0.078	0.496
	Visceral fat (log)	0.618	< 0.001
	Subcutaneous fat (log)	0.291	0.011
	Adjusted R ²	0.752	< 0.001
HOMA index (log)	Age	0.004	0.946
	Hepatic TG t (log)	0.100	0.362
	Visceral fat (log)	0.613	< 0.001
	Subcutaneous fat (log)	0.301	0.006
	Adjusted R ²	0.769	< 0.001
Systolic BP (log)	Age	0.328	0.001
	Hepatic TG (log)	0.177	0.220
	Visceral fat (log)	0.159	0.420
	Subcutaneous fat (log)	0.452	< 0.001
	Adjusted R ²	0.358	< 0.001
Diastolic BP (log)	Age	0.238	0.013
	Hepatic TG (log)	0.187	0.189
	Visceral fat (log)	0.207	0.284
	Subcutaneous fat (log)	0.534	< 0.001
	Adjusted R ²	0.379	< 0.001

7.3 Study III

In the total group of study participants, there were no significant distinctions regarding BMI, WC, systolic and diastolic BP or triglyceride concentrations between baseline and follow-up visits. Total cholesterol, LDL-cholesterol and HDL-cholesterol concentrations decreased while glucose concentration increased during follow-up (Table 9). All lifestyle factors assessed indicate a significant improvement: the number of smokers decreased, physical activity increased, and the number of soft fat users increased (Table 10). During the follow-up, the overall risk profile improved, as estimated by the CVD risk score, while the Framingham risk score indicated a worsening risk profile (Table 11).

Of the 200 men who took part in the two-year follow-up visit, data on educational attainment were available for 185 men. We categorised these men into three levels based upon their duration of formal schooling: low ≤ 9 years, $n = 31$ (16.8%); middle 10 to 12 years, $n = 87$ (47%); and high ≥ 13 years, $n = 67$ (36.2%). There were no statistically significant differences between the educational groups either at the baseline visit or at the follow-up visit in any of the clinical characteristics assessed (Table 9). Within the groups, some parameters improved, while others did not or even worsened. There was a reduction of 3.5% of total cholesterol in all groups. In the middle educational group, LDL-cholesterol decreased by 6.7% and less in the other groups. In the high educational group, triglycerides decreased 12.9%, but in the other groups, the change was in the opposite direction and not so prominent. HDL-cholesterol decreased in the low educational group by 17.6%, in the middle educational group by 12.2% and in the high educational group by 10.5%, respectively. The glucose concentration increased in the low and middle educational groups by 3.6% and in the high educational group by 5.5%, respectively. However, none of the changes within groups which have been described achieved statistical significance. In all groups, the change in BMI, WC and systolic and diastolic BP between visits was only marginal (Table 9).

Regarding lifestyle characteristics at the baseline, the use of soft fat among participants who belonged to the low educational attainment group was considerably lower than among participants in the other groups. The use of soft fat differed statistically significantly between the groups ($p = 0.019$). Other lifestyle factors evaluated did not vary markedly between the groups at the baseline visit. The results from the follow-up visit showed that the users of soft fat in the groups are closer and there is no longer any important distinction between the groups. Moreover, there was no statistically significant difference between the groups in the other lifestyle factors investigated. For all lifestyle factors, the changes within groups were in a desired direction and statistically significant, except in the low educational attainment group, where the increase of physical activity did not reach a statistically significant level. The most prominent change within the group was the increase of users of soft fat in the low educational attainment group (Table 10).

The overall CVD risk profile varied notably between the groups at baseline and at follow-up visits when assessed by the CVD risk score. At the baseline, the results displayed the least risk level in the high educational group. During follow-up, the risk level decreased in all the groups; however, it was the lowest in the high educational group. According to the Framingham risk score, the risk level

heightened during follow-up in the low and middle educational groups, while in the high educational group, the risk level remained unchanged (Table 11).

Table 9. Cardiometabolic risk factors at baseline and follow-up visits according to educational attainment groups

	Educational attainment			P value ^a	All n = 200	P value ^b
	Low n = 31	Middle n = 87	High n = 67			
BMI kg/m ²						
Baseline	29.9 (3.8)	29.3 (4.7)	29.2 (5.8)	0.804	29.4 (5.0)	0.183
Follow-up	30.2 (4.3)	29.7 (5.2)	29.0 (5.5)	0.482	29.6 (5.2)	
95% CI	-0.3 to 1.0	-0.1 to 0.8	-0.5 to 0.2		-0.1 to 0.4	
WC cm						
Baseline	105.2 (11.8)	102.0 (11.2)	101.4 (12.8)	0.371	102.7 (11.9)	0.591
Follow-up	105.0 (12.3)	103.0 (11.7)	100.5 (13.7)	0.171	102.9 (12.7)	
95% CI	1.7 to 1.4	-0.3 to 2.3	-2.2 to 0.5		-0.6 to 1.0	
SBP mmHg						
Baseline	141.9 (21.5)	136.7 (16.5)	137.4 (12.9)	0.296	137.8 (16.0)	0.578
Follow-up	141.2 (14.7)	138.2 (16.4)	137.4 ((15.2)	0.583	138.4 (15.5)	
95% CI	-8.0 to 6.4	-1.7 to 4.8	-3.7 to 3.7		-1.6 to 2.8	
DBP mmHg						
Baseline	92.0 (13.0)	90.7 (11.5)	91.3 (10.2)	0.741	91.1 (11.1)	0.198
Follow-up	90.2 (8.9)	90.0 (11.0)	90.0 (10.2)	0.996	90.1 (10.2)	
95% CI	-7.0 to 2.3	-3.1 to 1.7	-3.9 to 1.3		-2.7 to 0.5	
Total-C						
Baseline	5.6 (0.97)	5.6 (1.0)	5.7 (1.0)	0.802	5.6 (1.0)	0.003
Follow-up	5.4 (0.96)	5.4 (1.0)	5.5 (0.9)	0.830	5.4 (0.9)	
95% CI	-0.6 to 0.2	-0.4 to 0.0	-0.4 to 0.0		-0.3 to -0.1	

LDL-C						
Baseline	3.22 (1.00)	3.35 (0.91)	3.38 (0.91)	0.661	3.33 (0.91)	
Follow-up	3.08 (0.63)	3.12 (0.78)	3.29 (0.86)	0.340	3.16 (0.78)	0.002
95% CI	-0.49 to 0.22	-0.38 to 0.08	-0.27 to 0.08		-0.27 to -0.06	
HDL-C						
Baseline	1.48 (0.46)	1.48 (0.37)	1.43 (0.27)	0.811	1.48 (0.35)	
Follow-up	1.22 (0.34)	1.30 (0.32)	1.28 (0.27)	0.367	1.29 (0.33)	<0.001
95% CI	-0.39 to -0.14	-0.23 to -0.14	-0.19 to -0.11		-0.22 to -0.15	
TG						
Baseline	2.29 (1.20)	1.89 (1.65)	2.01 (1.39)	0.621	2.01 (1.52)	
Follow-up	2.39 (1.79)	1.98 (1.59)	1.75 (0.75)	0.104	1.98 (1.39)	0.130
95% CI	-0.30 to 0.65	-0.15 to 0.34	-0.55 to 0.03		-0.20 to 0.13	
Glucose						
Baseline	5.6 (1.0)	5.5 (0.5)	5.5 (0.6)	0.524	5.6 (0.6)	
Follow-up	5.8 (0.5)	5.7 (0.6)	5.8 (0.7)	0.743	5.8 (0.6)	<0.001
95% CI	-0.0 to 0.3	0.1 to 0.3	0.1 to 0.4		0.1 to 0.3	

Data are means (SD). ^a P = values are for testing equality between groups. ^b P = values are for testing paired differences. BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, Total-C = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol (mmol/l) and TG = triglycerides (mmol/l). 95% CI are changes of means between baseline and follow-up visits.

Table 10. Lifestyle characteristics at baseline and follow-up visit according to educational attainment groups

	Educational attainment			P value ^a	All n = 200	P value ^b
	Low n = 31	Middle n = 87	High n = 67			
Smoking %						
Baseline	71.0	59.8	50.7	0.170	59.5	0.001
Follow-up	64.5	54.0	41.8	0.092	52.0	
95% CI	-20.1 to 7.4	-13.8 to 2.5	-16.1 to -1.6		-12.3 to -2.6	
PA ≥ 90 min/wk%						
Baseline	9.7	10.3	17.9	0.357	13.5	<0.001
Follow-up	25.8	27.6	29.4	0.928	27.0	
95% CI	-0.15 to 33.6	8.4 to 26.5	0.9 to 22.9		7.6 to 19.5	
Users of soft fat%						
Baseline	3.4	23.5	12.1	0.019	18.0	<0.001
Follow-up	46.7	56.5	46.3	0.396	51.5	
95% CI	22.3 to 60.7	22.2 to 42.4	21.1 to 44.6		26.4 to 39.8	

PA = physical activity. ^a P = values are for testing equality between groups. ^b P = values are for testing the paired difference. 95% CI are for changes of means between baseline and follow-up visits.

Table 11. CVD risk score values at baseline and follow-up visits according to educational attainment groups

	Educational attainment			P value ^a	All n = 200	P value ^b
	Low n = 31	Middle n = 87	High n = 67			
CVD risk score						
Baseline	7.1 (1.7)	6.3 (1.6)	5.8 (1.1)	0.001	6.2 (1.5)	
Follow-up	6.6 (2.5)	5.7 (2.2)	4.8 (1.7)	<0.001	5.5 (2.1)	<0.001
95% CI	-1.3 to 0.4	-1.0 to -0.2	-1.5 to -0.6		-1.0 to -0.5	
Framingham score						
Baseline	10.3 (2.5)	9.3 (2.7)	9.5 (2.3)	0.174	9.6 (2.6)	
Follow-up	11.2 (2.8)	9.8 (2.7)	9.5 (2.6)	0.018	10.0 (2.8)	0.036
95% CI	-0.1 to 1.8	-0.1 to 1.0	-0.5 to 0.6		0.0 to 0.7	

Data are means (SD). ^a P = values are for testing equality between groups. ^b P = values are for testing the paired difference. 95% CI indicate changes of means between baseline and follow-up visits.

7.4 Study IV

During the five years of follow-up, there were 230 dropouts. At the baseline, there were no contrasts between the dropouts and those who continued in any of the risk factors assessed (all $p > 0.11$). The dropouts had a higher CVD risk score than those who continued (6.4 vs. 6.1), but the disparity was not statistically significant ($p = 0.46$). The mean follow-up time was 5.1 years (SD = 0.4). The results at follow-up were available for 159 subjects.

The men were divided into three groups based upon self-reported CVD monitoring visits during follow-up. Of these people, 34.6% (Group 1) had not visited healthcare providers for CVD monitoring between the baseline and follow-up, whereas 37.1% had made such visits at their primary healthcare centres (Group 2), and 28.3% had visited occupational healthcare (Group 3). Two men were followed up in private healthcare. For further analyses, these men were included in Group 3. There was minimal attendance in the group sessions provided at local healthcare centres as routine activities. Of the 12 men who joined the weight programme, seven belonged to group 2, and five, to group 3. Only one participant (group 3) took part in the smoking cessation programme.

In all, a positive family history for CVD was reported by 33.1% of the subjects, divided by group: 18.5% of the men in Group 1, 45.5% of the men in Group 2 and 40.3% of the men in Group 3. At the baseline, no subjects received antihypertensive, lipid-lowering or diabetes medication. During the follow-up, the medications for men in groups 2 and 3 were initiated by primary healthcare or occupational care physicians as follows: antihypertensive medications 40.7% and 26.7% ($p = 0.136$), respectively; lipid-lowering medication 23.7% and 8.9% ($p = 0.048$), respectively; and type 2 diabetes medication 10.2% and 2.2% ($p = 0.110$), respectively.

In the total group of study participants, BMI, WC and SBP were higher at the follow-up than at the baseline; the change was not significant. A statistically significant increase was seen only in glucose concentration. The lower values in LDL-cholesterol, triglycerides concentrations and DBP at follow-up did not diverge importantly from the values at baseline, whereas the decrease in HDL-cholesterol concentration reached statistical significance. The total cholesterol remained unchanged (Table 12). In all, for the three lifestyle factors evaluated, the

change was statistically significant (Table 13). The overall risk profile indicated improvement during the follow-up with both risk tools. The change was statistically significant with the CVD risk score but not with the SCORE Chart (Table 14).

None of the risk factors analysed indicated statistically significant disparities between the groups either at baseline or at follow-up (Table 12). Within the groups, the values of some parameters indicated improvement, while others worsened. A statistically significant change in the worse direction was seen in systolic and diastolic BP and in total cholesterol concentration in group 1. A statistically significant decrease in HDL cholesterol concentration was seen in all groups, with an increase in glucose concentrations in groups 1 and 3, respectively. The lowering of DBP and LDL cholesterol concentration in group 2 was the only statistically significant improvement among the risk factors (Table 12).

Even though lifestyle factors diverged to some extent between groups, there were no statistically significant differences between the groups in any of the lifestyle factors assessed, either at baseline or at follow-up. In all groups, within-group changes in all lifestyle factors assessed proved to be desirable and were statistically significant. The most prominent change was the increased number of users of soft fat (Table 13).

The overall CVD risk profile did not vary importantly between the groups at baseline regardless of the method used, the CVD risk score or the SCORE Chart. The changes in the risk profile within individual groups during the follow-up led to a statistically significant difference between the groups. In group 1, the risk level improved marginally during the follow-up when assessed by CVD risk score, while by SCORE Chart, the alteration in the risk level was reversed. In groups 2 and 3, there was a substantial decrease in the risk during the follow-up, as assessed by both risk scores; however, the change was statistically significant only by the CVD risk score (Table 14). The reduction of the risk level remained statistically significant even when analyses were limited to participants receiving no cardio-metabolic medications.

Table 12. Clinical characteristics at baseline and follow-up according to risk communication visits during follow-up

	Risk communication visits during follow-up				P value ^b
	No visits n = 55	Primary care n = 59	Occupational care n = 45	All n = 159	
BMI kg/m ²					
Baseline	29.1 (4.5)	30.2 (6.6)	29.0 (4.3)	29.5 (5.3)	0.001
Follow-up	29.7 (4.5)	30.6 (7.2)	29.9 (4.6)	30.1 (5.7)	
95% CI	-0.4 to -1.2	-0.2 to 1.1	0.3 to 1.5	0.3 to 1.0	
WC cm					
Baseline	101.7 (12.0)	105.9 (15.3)	103.1 (10.8)	103.7 (13.1)	0.128
Follow-up	103.0 (12.1)	105.7 (17.3)	104.8 (12.4)	104.5 (14.2)	
95% CI	-0.6 to 3.2	-2.0 to 1.5	-0.4 to 3.8	-0.2 to 1.9	
SBP mmHg					
Baseline	136.6 (15.1)	141.5 (18.7)	140.0 (15.9)	139.4 (16.7)	0.156
Follow-up	144.2 (18.6)	137.7 (14.9)	142.4 (14.7)	141.4 (16.4)	
95% CI	3.6 to 11.7	-8.0 to 0.4	-2.8 to 7.5	-0.7 to 4.5	
DBP mmHg					
Baseline	88.6 (9.5)	93.9 (12.8)	92.6 (9.9)	91.7 (11.1)	0.570
Follow-up	92.9 (10.6)	89.0 (8.9)	91.8 (9.8)	91.2 (9.9)	
95% CI	1.7 to 6.9	-8.0 to -1.8	-4.5 to 2.8	-2.4 to 1.3	
Total-C					
Baseline	5.6 (1.0)	5.6 (1.3)	5.5 (1.0)	5.5 (1.1)	0.666
Follow-up	5.8 (0.9)	5.3 (1.0)	5.4 (1.1)	5.5 (1.1)	
95% CI	0.0 to 0.4	-0.6 to 0.1	-0.3 to 0.2	-0.2 to 0.1	

LDL-C						
Baseline	3.26 (0.83)	3.20 (0.99)	3.27 (0.88)	0.841	3.24 (0.90)	
Follow-up	3.31 (0.78)	2.94 (0.85)	3.23 (0.94)	0.117	3.15 (0.86)	0.153
95% CI	-0.12 to 0.22	-0.50 to -0.03	-0.31 to 0.22		-0.22 to 0.03	
HDL-C						
Baseline	1.57 (0.46)	1.52 (0.36)	1.41 (0.34)	0.149	1.51 (0.39)	
Follow-up	1.42 (0.34)	1.36 (0.40)	1.29 (0.34)	0.262	1.36 (0.39)	<0.001
95% CI	-0.22 to -0.09	-0.24 to -0.07	-0.19 to -0.07		-0.19 to -0.11	
TG						
Baseline	1.72 (1.11)	2.14 (2.51)	2.03 (1.82)	0.498	1.96 (1.92)	
Follow-up	1.75 (1.04)	1.72 (0.96)	1.88 (2.86)	0.882	1.77 (1.72)	0.190
95% CI	-0.26 to 0.31	-1.07 to 0.22	-0.60 to 0.31		-0.47 to 0.09	
Glucose						
Baseline	5.5 (0.6)	5.7 (0.6)	5.6 (0.5)	0.123	5.6 (0.6)	
Follow-up	5.9 (0.8)	5.8 (0.8)	5.9 (0.7)	0.863	5.9 (0.8)	<0.001
95% CI	0.2 to 0.5	-0.1 to 0.3	0.1 to 0.4		0.1 to 0.3	

Data are means (SD). ^a P values are a test of equality between groups. ^b P are values for the paired difference. BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, Total-C = total cholesterol in mmol/l, LDL-C = low-density lipoprotein cholesterol in mmol/l, HDL-C = high-density lipoprotein cholesterol in mmol/l, TG = triglycerides in mmol/l, Glucose in mmol/l. 95% CI are for changes of means between baseline and follow-up visits.

Table 13. Lifestyle characteristics at baseline and follow-up according to risk communication visits during follow-up

	Risk communication visits during follow-up				P value ^a	All n = 159	P value ^b
	No visits n = 55	Primary care n = 59	Occupational care n = 45				
Smoking%							
Baseline	63.6	50.8	51.1			55.3	
Follow-up	50.9	37.3	40.0		0.309	42.8	<0.001
95% CI	-23.9 to -0.8	-23.4 to -3.1	-24.8 to 3.5			-19.2 to -5.7	
PA ≥ 90 min/wk%							
Baseline	36.4	22.0	28.9		0.241	28.9	
Follow-up	60.0	55.9	53.3		0.792	56.6	<0.001
95% CI	9.5 to 36.2	18.9 to 46.6	4.7 to 41.6			18.6 to 36.0	
Users of soft fat%							
Baseline	21.8	22.0	11.1		0.277	18.9	
Follow-up	72.7	84.7	73.3		0.246	77.4	<0.001
95% CI	35.5 to 62.3	46.6 to 73.6	45.5 to 73.9			49.7 to 65.5	

PA = physical activity. ^a P values are assessed for the test of equality between groups. ^b P are values for paired difference. 95% CI signify changes of means between baseline and follow-up visits.

Table 14. Risk scores at baseline and follow-up according to risk communication visits during follow-up

	Risk communication visits during follow-up				P value ^a	All 159	P value ^b
	No visits n = 55	Primary care n = 59	Occupational care n = 45				
CVD risk score							
Baseline	6.0 (1.7)	6.1 (1.7)	6.0 (1.4)		0.898	6.1 (1.6)	
Follow-up	5.9 (2.2)	4.8 (2.3)	5.4 (2.2)		0.027	5.4 (2.3)	<0.001
95% CI	-0.5 to 0.4	-1.9 to -0.8	-1.4 to 0.1			-1.1 to -0.4	
SCORE Chart							
Baseline	4.7 (1.7)	5.1 (2.2)	4.8 (2.2)		0.594	4.9 (2.1)	
Follow-up	5.2 (2.3)	4.0 (1.9)	4.3 (2.1)		0.010	4.5 (2.2)	0.060
95% CI	-0.1 to 1.1	-1.6 to -0.68	-1.3 to 0.3			-0.7 to 0.0	

Data are means (SD). ^a P values are for testing the equality between groups. ^b P values are for testing the paired difference. CVD risk score is a modified version of the North Karelia project risk tool. Score Chart: CVD risk extrapolated to age 60 by Score European Low Risk Chart ⁽³⁾. 95% CI are for changes of means between baseline and follow-up visits.

8 DISCUSSION

8.1 Study I

Abdominal obesity, often expressed as increased WC, is an independent predictor of cardiometabolic risk factors, such as dyslipidaemia, hyperglycaemia and hypertension ^(165, 166) as well as CVDs ^(167,168) and type 2 diabetes ^(169,170).

In our study, which included a community-based sample of 196 middle-aged men, 109 had a positive risk status, meaning either a CVD risk score ≥ 4.5 or a FINDRISC score ≥ 7 or both, hereinafter called a *positive risk*. A WC of ≥ 94 cm correctly detected 92 men (true positives) and correctly left undetected 68 men (true negatives). When calculated on the basis of these figures, the sensitivity, specificity, and positive and negative predictive values of the test were: 84.4% (95% CI 76.4% to 90.0%), 78.2% (95% CI 68.4% to 85.5%), 82.9% (95% CI 74.8% to 88.8%) and 80.8% (95% CI 70.3% to 87.1%), respectively.

The prevalence of a positive risk in the study's population is 109/196, that is 55.6%. Applying this test in another population depends on the prevalence of the positive risk in that population leading to other predictive values. Generally, using the same test in a population with a higher prevalence increases the positive predictive value, and the negative predictive value decreases, respectively. Conversely, using the same test in a population with a lower prevalence decreases the positive predictive value; the negative predictive value increases, respectively ⁽¹⁷¹⁾. Generalisability also requires considering that the relationships between WC and health outcomes are affected by variables such as sex, ethnicity and age ⁽¹⁷²⁾.

Generally, a high PPV and high NPV are desirable test characteristics, providing that false positives and false negatives are minimised ⁽¹⁷¹⁾. Our test meets this condition. With a PPV of 82.9% and an NPV of 80.8%, the number of false positives and false negatives was 19 and 17, respectively.

The lower the number of false positives, the less the unnecessary load on the healthcare system. Moreover, because men displaying false negatives are not necessarily guided to counselling, a lower number is desirable.

The medians of the CV risk and diabetes scores were at a lower level (3.5 for CVD risk score and 6 for FINDRISC) than the thresholds used. Using the thresholds

levels of ≥ 4.5 and ≥ 7 , we avoided the possibility that only one single risk factor could lead to a positive risk level in the test. The CVD risk score and FINDRISC consist of a total of 10 cardio-metabolic risk factors. The highest single diabetes risk score (5 points) is obtained by an individual who at least occasionally has an elevated glucose level or who has a first-degree relative with diabetes. The highest single CVD Risk Score (4 points) is obtained by heavy smoking (at least 30 cigarettes per day) or by having a total cholesterol ≥ 8.5 mmol/l.

As the outcome variable is set to a relatively low level, the test can identify subjects in the phase where lifestyle modifications still have an impact on major risk factors. Restoring risk factors to their former levels is increasingly difficult in societies today. Among middle-aged men, the weight loss achieved within five years significantly reduced their risk for CVD over the subsequent 15 years but only in considerably overweight younger men ⁽¹⁷³⁾. Even in adolescence (15 years of age), CVD risk factors are at higher level among those with a WC \geq 75th percentiles than among those with a WC \leq 25th percentiles ⁽¹⁷⁴⁾. A favourable risk profile early in life is associated with better health outcomes later in life ⁽¹⁷⁵⁾. Risk factor levels in adolescence have an important role in the pathogenesis of CHD ⁽¹⁷⁶⁾. It is questionable whether a risk assessment is correctly timed at middle-age; however, it does follow the recommendations of institutional authors ⁽¹³⁴⁾.

In conclusion, a WC measurement is an easy way to obtain reliable information on cardio-metabolic risks. A cut-off point for a WC of ≥ 94 cm proved to be a good screening test to detect those with increased risk for future CVD and/or type 2 diabetes among 40-year-old Finnish men. There are limitations for expanding this test in other populations and in women; however, it can be used more widely in screening for cardio-metabolic risks in middle-aged Finnish men. The implementation of this screening method challenges the whole primary healthcare team, including nurses and practitioners. Everyone is responsible for recording their results in the health record of the healthcare customer as a starting point for the further evaluation of cardio-metabolic risks and initiate, if necessary, lifestyle counselling practices.

8.2 Study II

The use of imaging techniques, such as computer tomography or magnetic resonance imaging, has demonstrated that an excess accumulation of visceral

adipose tissue is associated with an atherogenic lipoprotein profile independent of BMI and SAT ⁽¹⁷⁷⁾. It has been reported that an increase in VAT volume is associated with adverse changes in CVD risk factors, including triglycerides, HDL-cholesterol, blood glucose, BP and metabolic syndrome ^(178,179, 180) and an increased risk for CVD ⁽¹⁸¹⁾ and type 2 diabetes ^(182, 183).

We used the definition of MetS ⁽¹⁵⁸⁾ to divide the study population into two groups. The two groups diverged notably according to various cardiometabolic risk factors, as expected. Besides the risk factors included in the definition of MetS, total cholesterol, LDL-cholesterol, insulin and the HOMA index revealed notably higher values among those with MetS than among those without MetS. This also applies to hepatic triglyceride content as well as visceral and subcutaneous fat volumes. The association between hepatic TG content and visceral fat was significant respecting cardio-metabolic risk factors. The associations were stronger with visceral fat than with hepatic TG content. These findings confirm the previous results of Liu et al. ⁽¹⁸⁴⁾. Of all of the risk factors studied, the strongest association observed was that between visceral fat and WC. Other risk factors revealing a statistically significant association with visceral fat were age, BMI, systolic and diastolic BP, HDL-cholesterol, triglycerides, fasting plasma glucose, fasting plasma insulin and HOMA index.

In the 1990s, the authors of a study in which abdominal visceral adiposity was verified by computer tomography proposed the use of WC as an anthropometric equivalent to visceral adiposity ⁽¹⁰³⁾. The study demonstrated a high correlation between WC and plasma triglycerides and HDL-cholesterol levels, fasting glucose, findings from a glucose challenge test and insulin levels. In a study including 185 healthy men (not under treatment for CHD, dyslipidaemia, diabetes or endocrine disorders), a specific phenotype called the *hyper-triglyceridemic waist* was proposed and defined as follows: WC \geq 90 cm and fasting triglyceride level \geq 2.0 mmol/l. A WC \geq 90 cm distinguishes men with hyperinsulinemia and increased apolipoprotein B concentration from those with normal concentrations of both variables, whereas a fasting triglyceride concentration \geq 2.0 mmol/l identifies men with a small, dense LDL particles. The authors exhibited the functionality of the concept in another sample of 287 men with and without coronary artery disease (CAD) verified by angiography. Men with both elevated WC and TG levels were at increased risk of CAD compared with men with low WC and low TG levels ⁽¹⁸⁵⁾. The relationship between the hyper-triglyceridemic-waist phenotype and CAD has also been confirmed in a prospective population study. Compared to participants

with a WC < 90 cm and TG < 2.0 mmol/l, the risk for CAD increased in combinations of these variables as follows: participants with a WC < 90 cm and TG \geq 2.0 mmol/l, participants with a WC \geq 90 cm and TG < 2.0 mmol/l, and WC \geq 90 cm and TG \geq 2.0 mmol/l. The lattermost always had a higher risk ⁽¹⁸⁶⁾.

In our cross-sectional study, the regression analyses confirm that visceral fat is an independent predictor of triglycerides, HDL-cholesterol, fasting plasma glucose and insulin, and HOMA index. Regardless of the strong association of visceral fat with diastolic and systolic BP, it does not indicate predictive power for hypertension, unlike subcutaneous fat. However, there are (prospective) studies whereby visceral fat alone ⁽¹⁸⁷⁾ and both visceral and subcutaneous fat have been shown to predict hypertension in an overweight population ⁽¹⁸⁰⁾.

In conclusion, an initial risk assessment can be based on a single anthropometric measurement, WC. However, even though WC predicts traditional cardiovascular risk factors, it cannot be used on its own to properly assess the risk of an individual.

8.3 Study III

Socioeconomic status (SES) is one of the strongest predictors of (general) morbidity and mortality ^(188, 189). SES is a complex phenomenon often conceptualised as a combination of financial, occupational and educational influences ⁽¹⁹⁰⁾. Educational level is an eligible determinant to indicate inequality in the morbidity of type 2 diabetes ^(191, 192), the incidence of CVD ⁽¹⁹³⁾ and the prevalence of CVD risk factors ^(190,194,195). Educational attainment has been proposed as a determinant of SES unless the study's hypothesis specifies which dimension of SES should be chosen ⁽¹⁹⁰⁾.

In today's society, social inequality can be seen, for example in unhealthy lifestyles in people with lower educational levels. Among the adult population in Finland, the smoking prevalence has declined notably over decades, but the variations between socioeconomic groups are still considerable. Among low, middle and highly educated people, the smoking prevalence was 17%, 11% and 6%, respectively, in 2017 ⁽¹⁹⁶⁾.

During the study period of the present work (2006 to 2008), the smoking prevalence was approximately 35% among middle-aged men in Finland ^(197,198) and about 55% among the subjects in this study.

Of the study's participants, the proportion of smokers was highest in the low SES group, both at baseline and at follow-up. Although the proportion of smokers decreased in all groups during the follow-up period, the change was statistically significant only in the high SES group. After an 8.9% reduction from the baseline, the smoking prevalence was still 42%, which was higher than in the male population of the same age. The aim of the intervention in this study was a more comprehensive change in overall lifestyle, not just targeting smoking.

The success of smoking cessation is less likely among those with low education. The results of a study following a birth cohort through adulthood demonstrated that the lower educated had fewer short-term and long-term attempts to quit smoking and were less likely to succeed than their higher educated counterparts ⁽¹⁹⁹⁾. Cigarette consumption is greater and dependence stronger among the less educated than among highly educated smokers ⁽²⁰⁰⁾.

Leisure-time physical activity is known to reduce the risk of CVD and type 2 diabetes ⁽²⁰¹⁾. A protective effect against cardiovascular death was seen even at a light level of physical activity, independent of traditional cardio-metabolic risk factors. Daily, brisk walking of at least 30 minutes substantially reduces the risk of type 2 diabetes ⁽²⁰²⁾.

In our study, an increase of leisure-time physical activity was seen in all SES groups. The change during the follow-up was greater in the low and middle educational attainment groups than in the high educational attainment group. In the low educational attainment group, the change did not reach statistical significance. The general national goal for physical activity during the study was moderate to vigorous physical activity of at least 90 minutes per week. Notably, many men exceeded this level with an activity of 150 to 180 minutes per week. Despite the increase in physical activity in the study's groups, the activity level remained much lower than in the general male population of the same age, as seen in a national survey in which 55% in 2006 and 60% in 2008 were practising moderate to vigorous physical activity at least two to three times per week ^(197,198).

The use of unsaturated fat differed considerably between the groups at baseline. The intervention supported a significant increase in the use of unsaturated fat in all

groups. At the follow-up visit, independent of the education level, half of the participants reported that they had replaced saturated fat with unsaturated fat. The change was statistically significant in all groups. Among Finnish men of an age similar to the study's participants', 63% used margarine on bread, and 48% utilised vegetable oil for cooking in 2006. The corresponding figures were 65% and 51% in 2008 ^(197,198).

We observed that these middle-aged men with an elevated risk for CVD improved their lifestyles. The change was seen in all lifestyle factors assessed and in all SES groups. However, when focusing upon risk factors such as BMI, WC and BP, no improvement was observed. Alterations in lipoproteins can be observed in relation to changes in dietary fat ratios and presumed increase in intake of carbohydrates to compensate for the reduced intake of saturated fat. When part of dietary saturated fat is replaced by carbohydrates, triglyceride concentration increases, and HDL-cholesterol concentration decreases ⁽²⁰³⁾. Elevated total carbohydrate intake causes the same changes in triglyceride and HDL-cholesterol concentrations ⁽²⁰⁴⁾. The partial replacement of dietary saturated fat with polyunsaturated fat reduces total and LDL-cholesterol concentrations ⁽²⁰³⁾. When part of dietary saturated fat is replaced with monounsaturated fat, the effects on lipoproteins are almost the same as when replaced with polyunsaturated ⁽²⁰⁵⁾. All these fit well with our findings. In all groups, the proportion of users of unsaturated fat increased, and total, LDL- and HDL-cholesterol levels decreased. Unlike other groups, triglyceride levels declined in the high educational attainment group only. This can be seen as the result of better-controlled carbohydrate intake, which could also be associated with a slight decline in BMI in this group.

In all groups, fasting glucose concentrations tended to increase slightly, which can be interpreted as a normal increase in fasting glucose observed in association with increased age ^(206,207). We estimated the CVD risk of the study's participants with the CVD risk score and the Framingham risk score (FRS). Both scores can evaluate a CVD risk profile, representing an RR. The FRS is also suitable for predicting the 10-year risk of a CVD event. The positive impact of health counselling on the risk profile at all levels of educational attainment was seen at follow-up visits in the CVD risk score, while the FRS did not detect any change in the risk profile. A more sensitive feature of the CVD risk score compared to the FRS is probably partially because the CVD risk score incorporates a physical activity component and smoking is further assessed in nine categories, while the FRS has only two categories of smoking.

In conclusion, the present study showed that lifestyle counselling is feasible among 40-year-old men with an elevated risk for CVD. Regardless of the level of education, the impact of counselling on the CVD risk profile was substantial. From a practical perspective, our findings stress the importance of using the CVD risk profile to guide health counselling instead of only examining individual risk factors.

8.4 Study IV

Both randomised controlled trials and observational studies have shown that lifestyle counselling has a positive impact on CVD risk factors among high-risk people, although the results from a range of studies are inconsistent. In short-term studies comparing intensive lifestyle support with the usual care have successfully reduced risk when implemented in primary healthcare ^(208,209,210) and occupational healthcare ^(211,212). In the literature, there are also studies where lifestyle counselling did not succeed in improving the risk profile in short-term ⁽²¹³⁾ and long-term ⁽²¹⁴⁾ randomised studies.

In our research, all men comprised a uniformly high CVD risk group. Attitudes towards risk status varied considerably. An awareness of the elevated risk was inadequate to motivate all individuals to participate in risk factors monitoring visits. A notable part, more than one-third of the participants, did not attend a risk factor control visit between baseline and follow-up visits, whereas almost two-thirds spontaneously sought risk-factor monitoring during follow-up at either local healthcare centres or occupational healthcare. One distinctive background feature among the participants was a positive family history of CVD. A positive family history was more than twice as common among the participants who sought risk factor monitoring during follow-up.

A physician's recommendations were more effective among those who had a positive family history of CVD, as they were more likely to report preventive actions, having cholesterol measured and the use of medication. However, reports of lifestyle changes were less frequent ⁽²¹⁵⁾. Furthermore, physicians' recommendations have been found to be associated with a higher likelihood of reported changes in diet and physical activity ⁽²¹⁶⁾. Family history can be used to personalise the health message and thereby enhance the individual's motivation to adopt a healthy lifestyle. However, the evidence of the effectiveness of this activity

is very limited ⁽²¹⁷⁾. A family history of premature CHD is of great importance. At 45 years of age, men with a family history of premature CHD had a 56% higher lifetime risk for CVD mortality compared to men without a family history of premature CHD ⁽²¹⁸⁾.

In the present study, we observed that risk-factor monitoring visits with primary healthcare and occupational healthcare providers led to desirable changes in lifestyle factors and lower CVD risk scores. Additionally, some cardio-metabolic risk factors improved. Blood pressure and lipids were better controlled among those who continued visits to their primary healthcare centre. It must be considered that the group continuing in primary healthcare benefited from more active treatment, as they received more cardio-protective medications than did those who received treatment at their occupational healthcare. In both groups that continued risk factor control visits, their overall risk status improved when they were assessed by the CVD risk score and the SCORE Chart. For those without such a visit, no improvement was seen, despite self-reported improvements in all lifestyle factors assessed. When evaluating the sub-population, that is men without cardio-protective medications that were followed up in primary healthcare, lifestyle changes alone significantly decreased their overall risk, as assessed with the CVD risk score and the SCORE Chart.

As the initial baseline risk assessment and health counselling sessions took place in primary healthcare centres, nurses and physicians in these centres were likely better prepared to guide the participants.

In all lifestyle factors assessed, the improvement was statistically significant in all groups. For comparison, among Finnish men, smoking prevalence was 24% in 2006 and 22% in 2011. Regarding physical activity, moderate to vigorous intensity exercise at least two to three times per week was 63% in 2006 and 67% in 2011, and consumption of unsaturated fat was 64% in 2006 and 60% in 2011 ^(219, 220). At the follow-up, the prevalence of smoking remained among study participants twice as high as in the general male population, but the decrease was distinct. Study subjects almost reached the level of physical activity of the general male population at follow-up, even though they started from a much lower level at baseline. Despite the study's participants' minor consumption of unsaturated fat at baseline, their use exceeded that of the general male population at follow-up.

Risk assessment methods are available to calculate global short-term (generally 10 years) CVD risk estimates. These methods are based on established CVD risk

factors, including age, hypertension, lipids and smoking. A new method has been published based on lifestyle, including smoking, BMI, physical activity, dietary intake and alcohol consumption. This method is called the Healthy Heart Score (HHS), and it was developed to serve as a tool for the long-term prevention of CVD. It is especially applicable for a population without traditional risk factors (usually the younger population), that is a screening tool for primordial prevention ⁽²²¹⁾.

The Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study showed that adherence to the AHA's ideal cardiovascular health concept ⁽²²²⁾ throughout childhood predicted vascular health in adolescence ⁽²²³⁾. Although it is desirable to avoid risky behaviours and risk factors in adolescence, there is a window of opportunity for intervention in the transition from youth to adulthood to modify one's trajectory from high risk in adolescence to low risk in adulthood ⁽²²⁴⁾.

In a study of young women, a higher HHS at baseline was associated with a significantly greater risk of developing risk factors such as diabetes, hypertension and hypercholesterolaemia during 20 years of follow-up ⁽²²⁵⁾. A follow-up study of two middle-aged cohorts (women between 1984 and 2010 and men between 1986 and 2010) proved that participants with HHS in the fifth versus the first quintile had significantly greater risk of death due to CHD, stroke and several cancers ⁽²²⁶⁾.

We compared the risk factor status of our study's participants to the results of a U.S. population survey, which estimated lifetime risk for CVD at age 50 and classified CVD risk into low and high categories, according to BP, total cholesterol, diabetes and smoking status ²²⁷. We found that, at a follow-up visit, 12 participants of those 59 who achieved a CVD risk score level of < 4.5 had a low lifetime risk for CVD and all the others had a high lifetime risk. According to the aforementioned survey, men with an SBP between 140 mmHg and 159 mmHg or DBP between 90 mmHg and 99 mmHg or total cholesterol between 200 mg/dl (5.18 mmol/l) and 239 mg/dl (6.19 mmol/l) have a lifetime risk for CVD of 46%. The lifetime risk for CVD increased to 50% when one of these cut-offs was exceeded and to 69% when two of these cut-offs were exceeded or if individuals have diabetes or were current smokers. Among our study's participants, 27% had a lifetime risk of 46%, 40.9% had a lifetime risk of 50%, and 24.5% had a lifetime risk of 69%.

During the study's period, according to SCORE Chart, none of the participants in the present study exceeded a high short-term risk level. At the follow-up visit,

according to the SCORE relative risk table, 17.1% of the study's participants had a risk equal to a person with all risk factors at an optimal level, while 16.5% had a five-time higher risk than that. The rest were in between.

The European Guidelines do not recommend that the decision for lifelong preventive treatment be based on the lifetime risk in people with low short-term risk. Such a situation should signal the need for active lifestyle advice and the awareness that starting drug treatments may need to be considered later in life ⁽¹³⁴⁾.

In conclusion, the modification of non-optimal lifestyles is a key issue in the primordial and primary prevention of CVD. The evaluation of lifestyles for preventive purposes is important at an early age and, at the latest, in middle age. Maintaining optimal lifestyles will prevent risk factors from increasing to a detrimental level or at least postpone it. From middle age onward, it is necessary to control cardio-metabolic risk factors alongside lifestyle monitoring. A positive family history of premature CVD should act as an alarm throughout the lifespan for all preventive actions.

9 STRENGTHS AND LIMITATIONS

Although a randomised controlled study design is considered methodologically more advanced than an observational study design, we decided to choose an observational design for our research. This is primarily because for ethical reasons; it would have been unethical to refuse health counselling from the control group. The homogeneity of the participants' age, gender and ethnicity can be seen as one of the strengths of our study. In addition, the validity of the results is supported by the fact that all participants underwent the same risk factor assessment and received the same health counselling during the baseline visit. Furthermore, another main strength of our study can be considered to be the natural course of follow-up. That is, participants spontaneously initiated risk monitoring visits during the study period.

A common limitation in the sub-studies was the relatively small number of participants in each study, which was especially the case in sub-studies III and IV. This was primarily due to the lack of willingness to participate in the initial screening visit and the considerably high percentages of drop-outs during the follow-up. In study I, the application of our test to other populations is limited by the fact that the predictive values depended on the prevalence of abnormality in the population being tested. In study II, the cross-sectional design of the study limited the ability to infer causality between the observed associations. In studies III and IV, because we studied Finnish men aged 40 years, caution should be warranted when generalising the results to age groups or ethnic groups other than Caucasians. Although our study did not include women, the method has been successfully applied to middle-aged women for preventive purposes in occupational healthcare (228).

In 2006, the initial invitation was addressed to all men born in 1966 and living in Helsinki. Of this population, 34% accepted the invitation and took part in a screening visit. The number of subjects declined further when 47% of potential participants invited to a two-year follow-up visit accepted the invitation. Subsequently, 41% of potential participants invited to a five-year follow-up visit accepted the invitation. These dilutions of potential participants at each stage of the study are likely to weaken its strength. In a primary prevention programme in England, the National Health Service offered cardiovascular risk assessments to

adults aged 40 to 74 years ⁽²²⁹⁾. Participation depended on the method of the invitation: invitation by a formal letter, 30.9%; invitation by a personalised letter, 31.3%; and invitation by a telephone call, 47.6%. Participation figures in our study were comparable with these.

10 CONCLUSIONS AND FUTURE DIRECTIONS

Various methods can be used to evaluate CVD and diabetes risk profiles starting with the WC measurement and proceeding to a complex risk factor measurement or lifestyle assessment as well as combinations of these. The significance of the identified risk profile depends on the life-cycle phase. The harmful consequences of risk factors when found in childhood are more likely to be preventable than those observed in older people. In adolescence, the impact of risk factors on the circulatory system will be in the future, while in the elderly, some consequences may already have been manifested. When risk factors call for intervention in middle-age and younger people, mostly at the start, it is a matter of lifestyle modification. Among older people, especially among those with a high short-term risk in addition to lifestyle changes, often medication is also needed as a prevention measure.

We found that visceral fat is an independent predictor of a cluster of metabolic risk factors and that it is strongly associated with WC. Our study also showed that the measurement of WC is a feasible screening tool among 40-year-old men to identify those who are at increased risk for CVD and/or type 2 diabetes. However, a waistline above the cut-off value alone does not provide enough information to initiate comprehensive risk communication. Nevertheless, it should trigger a more profound risk profile evaluation.

Regardless of the socioeconomic status and whether the participants continued risk monitoring visits, all participants showed improvement in all lifestyle factors assessed. Among those with low socioeconomic status and those who neglected risk monitoring visits, lifestyle changes were not sufficient to achieve a statistically significant overall CVD risk reduction, as among those with higher socioeconomic status and those who continued risk monitoring visits. Although the reasons for the range of behaviours of the study's participants during the follow-up period are beyond our study's questions, our observations emphasise the consideration of social inequality and stress the importance of easy access to continuous support and guidance.

According to clinical guidelines and good clinical practice, comprehensive CVD and diabetes risk assessments should be implemented at the earliest in middle age; individual abnormal risk factors and harmful lifestyle habits should be addressed

throughout the lifespan. The longer the duration of adverse risk factors or an unhealthy lifestyle, the more likely one is to develop CVD, diabetes and other related outcomes.


In the primary prevention of CVD, there are two key issues: to identify individuals at risk and to motivate them to maintain lifestyle changes in the long term. Our five-year follow-up study showed that, with a practice introduced in Helsinki, a favourable outcome can be achieved.

The screening programme started in Helsinki in 2006, and it has continued in a modified form since 2015. In the modified screening method, subjects complete an online health check questionnaire. Those with moderately elevated risk are directed to take part in appropriate risk management programmes. Those with a high risk receive an invitation to the office for a more in-depth investigation. In the modified screening method, age and gender are included as risk factors, which enable the expansion of the use of the screening method. The internet-based health check, including risk assessment, offers an opportunity for more extensive research use in the future.

Alongside the high-risk approach, a population-wide strategy is needed. As means, large-scale health education should begin as early as the child welfare clinic and continue in schools and other institutions, complemented with related information disseminated via the media. Other means include, for example, food labelling to make healthy choices easier, tobacco and alcohol taxation, and an environment that encourages physical activity. The ultimate goal is to change social norms and environments to support healthier behaviour.

11 APPENDICES

11.1 Appendix 1

 Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

1. Age

0 p. Under 45 years
2 p. 45–54 years
3 p. 55–64 years
4 p. Over 64 years

2. Body-mass index
(See reverse of form)

0 p. Lower than 25 kg/m²
1 p. 25–30 kg/m²
3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs
(usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94–102 cm	80–88 cm
4 p.	More than 102 cm	More than 88 cm

6. Have you ever taken medication for high blood pressure on regular basis?

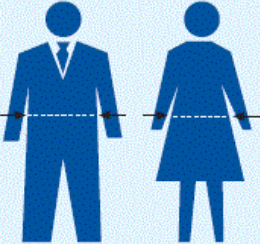
0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?

0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?

0 p. No
3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister or own child



4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?

0 p. Yes
2 p. No

5. How often do you eat vegetables, fruit or berries?

0 p. Every day
1 p. Not every day

Total Risk Score

The risk of developing type 2 diabetes within 10 years is

Lower than 7	Low: estimated 1 in 100 will develop disease
7–11	Slightly elevated: estimated 1 in 25 will develop disease
12–14	Moderate: estimated 1 in 6 will develop disease
15–20	High: estimated 1 in 3 will develop disease
Higher than 20	Very high: estimated 1 in 2 will develop disease

Please turn over

Test designed by Professor Jaakko Tuomilehto, Department of Public Health, University of Helsinki, and Jaana Lindström, MFS, National Public Health Institute

WHAT CAN YOU DO TO LOWER YOUR RISK OF DEVELOPING TYPE 2 DIABETES?

You can't do anything about your age or your genetic predisposition. On the other hand, the rest of the factors predisposing to diabetes, such as overweightness, abdominal obesity, sedentary lifestyle, eating habits and smoking, are up to you. Your lifestyle choices can completely prevent type 2 diabetes or at least delay its onset until a much greater age.

If there is diabetes in your family, you should be careful not to put on weight over the years. Growth of the waistline, in particular, increases the risk of diabetes, whereas regular moderate physical activity will lower the risk. You should also pay attention to your diet: take care to eat plenty of fibre-rich cereal products and vegetables every day. Omit excess hard fats from your diet and favour soft vegetable fats.

Early stages of type 2 diabetes seldom cause any symptoms. If you scored 12–14 points in the Risk Test, you would be well advised to seriously consider your physical activity and eating habits and pay attention to your weight, to prevent yourself from developing diabetes. Please contact a public-health nurse or your own doctor for further guidance and tests.

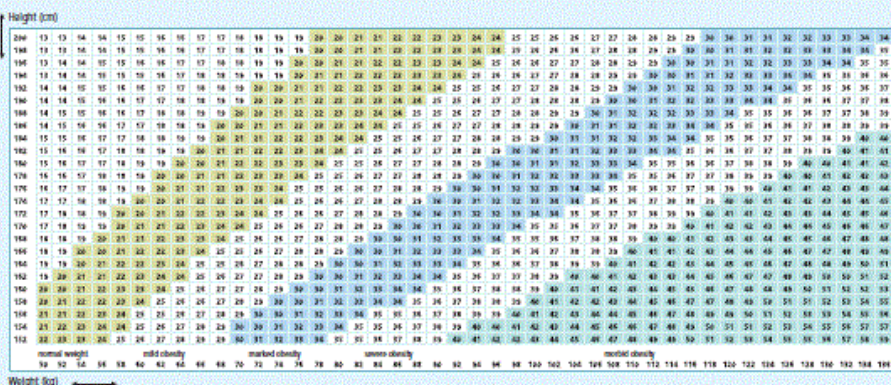
If you scored 15 points or more in the Risk Test, you should have your blood glucose measured (both fasting value and value after a dose of glucose or a meal) to determine if you have diabetes without symptoms.

BODY-MASS INDEX

The body-mass index is used to assess whether a person is normal weight or not. The index is calculated by dividing body weight (kg) by the square of body height (m). For example, if your height is 165 cm and your weight 70 kg, your body-mass index will be $70/(1.65 \times 1.65)$, or 25.7.

If your body-mass index is 25–30, you will benefit from losing weight; at least you should take care that your weight doesn't increase beyond this. If your body-mass index is higher than 30, the adverse health effects of obesity will start to show, and it will be essential to lose weight.

BODY-MASS INDEX CHART



11.2 Appendix 2

Liite 2a

Riskipistetaulukko

Pisteet	BMI kg/m ²	Tupakointi	Liikuntatottumukset*	Systolinen RR mmHg	Diastolinen RR mmHg	Kokonaiskolesteroli mmol/l
0	-24.9	0	≥3x/viikossa	-129	-79	-4.9
0.5	25-26.9	satunnaisesti	1-2x/viikossa	130-139	80-89	5.0-5.4
1.0	27-28.9	1-4/vrk	n. 1x/viikossa	140-149	90-94	5.5-5.9
1.5	29-30.9	5-9	Joskus	150-159	95-99	6.0-6.4
2.0	31-	10-14	Ei koskaan	160-	100-	6.5-6.9
2.5		15-19				7.0-7.4
3.0		20-24				7.5-7.9
3.5		25-29				8.0-8.4
4.0		30-				8.5-

* mitä tahansa liikuntaa, joka kestää yli 30 minuuttia yhtäjaksoisesti niin, että hikoilee ja hengästyy

Riskipisteet yhteensä	
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≥ 4.5 = kohonnut sydän- ja verisuonitautiriski

pisteet	riski
0-2.0	pieni
2.5-4.0	jonkin verran
4.5-7.0	melko suuri
7.5-11.0	suuri
11.5-16.0	erittäin suuri

- 1) Pohjois-Karjala -projekti, Kansanterveyslaitos
- 2) Suomen Sydäntautiliitto, Lääkintöhallitus, Kansanterveyslaitos, Suomen Kardiologinen Seura. Sepelvaltimotaudin ehkäisyyn suuntaviivat. Suomen Sydäntautiliitto ry 1986. Kokkola: Keski-Pohjanmaan Kirjapaino Oy, 1986.
- 3) Ketola E. Cardiovascular disease risk factors challenging primary care. The quality of risk factor recording and early prevention in primary care. Helsinki 2001.

Sydän- ja verisuonitautien riskitekijäkartoitus

Nimi _____ Sotu _____ Pvm _____

1. Ikä _____

2. Sukupuoli _____ 1 Nainen 2 Mies

3. Ammatti _____

4. Paino _____ 5. Pituus _____

6. Onko suvussa vanhemmalla/sisaruksilla/lapsella?

Sepelvaltimotautia	<input type="checkbox"/> kyllä	<input type="checkbox"/> ei	<input type="checkbox"/> ei tietoa
Diabetesta	<input type="checkbox"/> kyllä	<input type="checkbox"/> ei	<input type="checkbox"/> ei tietoa
Kohonnutta verenpainetta	<input type="checkbox"/> kyllä	<input type="checkbox"/> ei	<input type="checkbox"/> ei tietoa
Aivohalvausta	<input type="checkbox"/> kyllä	<input type="checkbox"/> ei	<input type="checkbox"/> ei tietoa
Kohonneita kolesteroliarvoja	<input type="checkbox"/> kyllä	<input type="checkbox"/> ei	<input type="checkbox"/> ei tietoa

7. Tupakointi

0 en tupakoi 1 kyllä, yhteensä _____ vuotta

Mikäli vastasitte kyllä, tupakoitte nykyisin?

☐ en lainkaan
☐ hajanaisesti
☐ 1-4 savuketta/pv
☐ 5-9 savuketta/pv
☐ 10-14 savuketta/pv
☐ 15-19 savuketta/pv
☐ 20-24 savuketta/pv
☐ 25-29 savuketta/pv
☐ 30 savuketta tai enemmän/pv
☐ piippua/sikaria

8. Käyttätkö alkoholipitoisia juomia?

☐ en lainkaan
☐ kerran/kk tai harvemmin
☐ 2-4x/kk
☐ 2-3x/vko
☐ 4x/vko tai useammin

Mikäli vastasitte käyttävänne alkoholia, kuinka monta annosta juotte kerrallaan?

☐ 1-2 annosta
☐ 3-4 annosta
☐ 5-6 annosta
☐ 7-9 annosta
☐ 10 annosta tai enemmän

9. Onko Teillä diabetesta = sokeritautia?

☐ ei diabetesta
☐ dieettihoitoinen diabetes
☐ tablettihoitoinen diabetes
☐ insuliinihoitoinen diabetes
☐ tabletti- ja insuliinihoitoinen diabetes

10. Onko Teillä verenpainetauti tai muita sydän- ja verisuonisairauksia? Mitä?

11. Mitä lääkkeitä käytte säännöllisesti? Nimet ja annokset?

12. Harrastatteko liikuntaa (= mitä tahansa liikuntaa, joka kestää yli 30 minuuttia yhtäjaksoisesti niin, että hikoilee ja hengästyy?)

☐ 3x viikossa tai enemmän
☐ 1-2x/vko
☐ n. 1x/vko
☐ joskus
☐ ei koskaan

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